Chapter 4

Therapy-Related Acute Myeloid Leukemias

Margarita Guenova, Gueorgui Balatzenko and Georgi Mihaylov

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52459

1. Introduction

Therapy-related acute myeloid leukemia (t-AML) is a heterogeneous group of myeloid neoplasms occurring as an overwhelming complication in patients receiving previous cytotoxic chemotherapy and/or radiation therapy used to treat haematopoietic or solid malignancies or associated with immunosuppressive treatment for non-neoplastic rheumatologic/autoimmune diseases or solid organ transplantation (Offman et al., 2004; Kwong, 2010). T-AML is an increasingly recognized condition included in the category of therapy-related myeloid neoplasms in the revised WHO classification of tumours of haematopoietic and lymphoid tissues, together with therapy-related myelodysplastic syndrome (t-MDS) and myelodysplastic/myeloproliferative neoplasm, that constitute a unique clinical syndrome (Vardiman et al., 2009).

The average age of the population in the developed countries is increasing, and cancer incidence increases with age. Both improved early detection of first malignancies and primary oncologic therapy have led to enhanced survival rates, and the risk of t-AML has consequently risen over the last few decades (Travis, 2006; Ries et al., 2008). Thus patients are, in a sense, the fortunate victims of our own success. Secondary leukemias challenge both the understanding of leukemogenesis and the clinical management of these conditions. The disease offers a unique opportunity to study leukaemic transformation by relating specific genetic and molecular abnormalities to the biologic effects of particular agents. The detailed insights into pathogenetic mechanisms will eventually help to establish a more differentiated clinical approach to successfully treat, but hopefully also prevent, these often fatal consequences of cytotoxic therapies. Despite that t-AMLs share common phenotypic features with de novo AML, the prognosis is generally unfavorable.

In general, t-AML are of particular importance to study for several reasons: (i) they represent the most serious long-term complications to current cancer therapy and the understanding would help to identify patients at risk in order to tailor therapy; (ii) they can be directly induced by chemically well-defined agents or irradiation with well-known cellular effects; (iii) they present the same chromosome aberrations and gene mutations as de novo AML, allowing for extrapolation of results from one to the other type of disease thus clarifying the biological processes leading to leukemogenesis; (iv) an early stage of MDS with refractory cytopenia is often diagnosed in therapy-related diseases, because most patients are followed thoroughly after intensive chemotherapy or irradiation, while in *de novo* AML, such information is often lacking; (v) there is still no consensus on the therapeutic management.

2. Epidemiology

The proportion of therapy-related AMLs varies from 5% to higher than 10% out of all cases of AMLs depending on the primary disease and the applied treatment in regard to chemical structure and dose of the used compounds, as well as to the type and intensity of used physical agent (Schneider et al., 1999). The GIMEMA registry reports an incidence of 5% of AML occurring as a second malignancy in Italy, however this registry includes only patients in whom treatment is feasible. Similarly, t-AML account for about 6% of all new AML cases in the UK, thus corresponding to an incidence rate at around 0.2/100 000/year (reviewed in Seedhouse & Russell, 2007). For a 12-years period, the review of our own data also showed that in 26 out of 407 consecutive cases of adult AML diagnosed and treated in our institution had a history for a previous malignancy treated with chemotherapy and/or radiotherapy which accounts for 6,1% (Balatzenko & Guenova, 2012). Higher values were reported by others as the pooled analysis of a consecutive series of 372 Swedish adult AML cases compared to 4230 unselected cases reported in the literature 1974 – 2001 revealed an incidence of 13% and 14%, respectively (Mauritzson et al.,2002).

2.1. Age

All age groups are affected - both children and adults develop AML following treatment with antineoplastic agents. However, children deserve particular consideration, taking into account the long life-expectancy of oncological patients cured by chemo and radiotherapy (Le Deley et al., 2003). As demonstrated in the published literature, the risk of developing AML following chemotherapy is not reliably correlated with the age of the pediatric patient. There is no consistent evidence that indicates that younger children will be at increased risk; in fact, some studies suggest that younger children might actually display a decreased susceptibility. Unlike secondary solid tumors such as breast, central nervous system, bone, and thyroid cancer which are highly dependent on the age of the patient at time of diagnosis and treatment; an age dependency for t-AML risk was not observed in the same pediatric patient populations (reviewed in Pyatt et al., 2007). In addition, though in the Guidelines for Carcinogen Risk Assessment (2005), presented at the Risk Assessment Forum U.S. Environmental

http://dx.doi.org/10.5772/52459

Protection Agency a 10-fold higher risk attributable to early-life carcinogenic exposure was assumed, leading to a reasonable expectation that children can be more susceptible to many carcinogenic agents, the available scientific and medical literature does not support the hypothesis that children necessarily possess an increased risk of developing AML following leukemogenic chemical exposure (Pyatt et al., 2007, Barnard et al, 2005).

In adult patients there is a higher risk and shorter latency period for the development of t-AML (Dann et al., 2001). In general, there is no convincing evidence for gender predisposition (Pagano et al., 2001; Smith et al. 2003).

2.2. Primary malignancies

Due to decreasing overall death rates in cancer there is an increasing number of cured patients at risk of developing t-AML. The review of reports on long follow-up of high numbers of patients treated with relatively uniform protocols comprising cytotoxic drugs, growth factors and radiation therapy individually or in combination highlights the major trends, with the greatest likelihood of developing therapy-related myeloid neoplasms following treatment of hematopoietic malignancies and breast cancer in adults, ALL and central nervous system tumors in children, germ cell tumours, lung cancer, etc. A significant proportion of t-AMLs nowadays involve patients treated for non-neoplastic disorders, and those treated with high-dose chemotherapy followed by autologous stem cell transplantation (Mauritzson et al., 2002; Suvajdžić et al. 2012; Ramadan et al., 2012). Representative studies are summarised in Table 1 demonstaring the incidence of t-AML in different primary diseases.

2.2.1. Hematologic malignancies

Up to 10% of patients with a preceeding lymphoid neoplasm treated with conventional chemotherapy and especially high-dose therapy and autologous stem cell transplantation may develop a t-AML within 10 years following primary therapy (Table 1). In patients with Hodgkin lymphoma (HL), the risk of t-AML has been reported to range between 1% and 10%, depending on the type of therapy administered, the study population size, and the follow-up duration. In patients with non-Hodgkin's lymphoma (NHL), an increased risk of secondary malignancies including therapy-related myeloid neoplasms has been reported, in particular when fludarabine-containing regimens or SCT are used. Significant risk factors were older age at the time of diagnosis, male sex, and fludarabine- or nucleoside analogs-containing therapy or SCT.Interestingly, leukemia cases are rarely or never seen in patients treated with radiotherapy alone (Mudie et al. 2006). Secondary carcinogenesis remains a major late complication in patients with acute lymphoblastic leukemia, particularly in children. A retrospective study of the cumulative incidence of secondary neoplasms after childhood ALL over 30 years showed that the risk of t-AML is higher in ALL children who receive a high cumulative dose and prolonged epipodophyllotoxin therapy in weekly or bi-weekly schedules, with short-term use of G-CSF and central nervous system irradiation as additive risk factors (Hijiya et al.,2007).

Primary Disease	Number of patients in the study	Number of patients with t-AML	Therapy	Median Latency	References
Hematological Malignancies					
Acute lymphoblastic leukemia (adults)	641	6 (0.9%)	CT	32 months	Verma et al.,2009
Acute lymphoblastic leukemia (children)	733	13 (1.8%)	CT	3 years	Pui et al.,1989
Acute lymphoblastic leukemia (children)	1290	37 (2,9%)	CT	3.8 years	Hijiya et al., 2007
Acute lymphoblastic leukemia	1494	6 (0.4%)	CT	1.3 years	Tavernier et al.,2007
CLL	521	3 (0.6%)	CT	34 months	Morrison et al.,2002
B-NHL; T-NHL; Hodgkin's lymphoma	1347	11 (0.8%)	HDCT± MoAbs		Tarella et al.,2011
NHL	230	11 (4.8%)	HD CT + RT	4.4 years	Micallef et al.,2000
NHL	29153	29 (0.1%)	RT ± CT; other	61 months	Travis et al.,1991
Hodgkin's lymphoma	5411	36 (0.7%)	RT ± CT	5 years	Josting et al.,2003
Hodgkin's lymphoma	2676	17 (0.6%)	RT; CT; RT +CT	79.9 months	Devereux et al.,1990
Hodgkin's lymphoma	29552	143 (0.5%)	RT; CT; RT +CT	ND	Kaldor et al.,1990
Hodgkin's lymphoma	947	23 (2.4%)	RT; CT; RT +CT	58 months	Cimino et al. ,1991
Hodgkin's lymphoma	32591	169 (0.5%)	RT; CT; RT +CT	ND	Dores et al.,2002
Hodgkin's lymphoma (children)	1380	24 (1.7%)	RT; CT; RT +CT	ND	Bhatia et al.,1996
Hodgkin's lymphoma	794	8 (1.0%)	RT; RT+CT	5 years	Mauch et al., 1996
Multiple Myeloma	8740	39* (0.4%)	CH, HDM-ASCT, IMiDs	45.3 months	Mailankody et al.,2011
Multiple Myeloma	2418	5 (0.2%)	CH, HDM-ASCT, IMiDs	ND	Barlogie et al.,2008
APL	77	3 (3.9%)	CT ± ATRA		Latagliata et al.,2002
Solid Tumors					
Small cell lung carcinoma	158	3 (1.9%)		2.7 years	Chak et al.,1984
Germ-cell tumours	212	4 (1.9%)	CT	ND	Pedersen-Bjergaard et al.,1991

http://dx.doi.org/10.5772/52459

Primary Disease	Number of patients in the study	Number of patients with t-AML	Therapy	Median Latency	References
Germ-cell tumours	442 174 124	3 (0.7%) 3 (1.7%) 0	CT RT+CT RT	ND	Schneider et al.,1991
Germ-cell tumors (children)	716 416	6 (0.84%) 0	CT+RT RT or S	101 weeks	Schneider et al.,1999
Ovarian Cancer	63359	109 (0.2%)	CT	4 years	Vay et al.,2011
Ovarian Cancer	99113	95 (0.1%)	RT; CT; RT +CT	4-5 years	Kaldor et al.,1990
Ovarian Cancer	28971	1 (0.003%) 65 (0.2%) 25 (0.09%)	RT CT RT+CT	3.3 years	Travis et al.,1999
Breast Cancer	5299 646	27 (0.5%) 5 (0.8%)	CT RT	ND	Fisher et al.,1985
Breast Cancer	82700	74 (0.09%)	CT; RT; CT +RT	5 years	Curtis et al.,1992
Breast Cancer	1474	14 (0.9%)	CH ± RT	66 months	Diamandidou et al., 1996
Testicular Cancer	1909	3 1 2	CT RT RT+CT	7.7 years	van Leeuwen et al., 1993
Testicular Cancer	28843	27 (0.09%)	CH; RT	ND	Travis et al.,1997
Prostate Cancer	487	3 (0.6%)	CH	48 months	Flaig et al.,2008
Prostate Cancer	168612	184 (0.1%)	RT		Ojha et al., 2010
Auto-immune diseases					
Reumatoid arthritis	53067	68 (SIR=2,4)		ND	Askling et al. 2005
Reumatoid arthritis	4160	0 (SIR=0)	TNF antagonist	NA	Askling et al. 2005
Multiple sclerosis	2854	21(SIR=1,84)		NA	Martinelli et al. 2009
Systemic lupus erythematodis	5715	8(OR=1,2)		ND	Loststrone et al. 2009
Wegener's granulomatosis	293	(SIR=19,6)		6,8-18,5 yrs	Faaurschou et al. 2008
Ulcerative colitis	2012	(OR=3,8)		ND	Johnson et al. 2012

Legend: * including terapy-related MDS; ND – no data; CT – chemotherapy; RT – radio therapy; IMiDs – Immunomodulatory drugs; MoAbs – monoclonal antibodies; HD – high dose; ASCT - autologous stem cell transplantation; ND – no data; S – surgery; ATRA - all-trans retinoic acid; NHL – non-Hodgkin's lymphoma; APL – acute promyelocytic leukaemia; OR – odds ratio; SIR – standardized incidence ratio.

Table 1. Representative studies of the incidence of t-AML in different primary diagnoses.

2.2.2. Solid tumours

In most studies, an increased risk of t-AML was reported in breast cancer patients treated with chemoradiotherapy ± radiotherapy. Besides, an increased incidence of t-MDS/AML in patients treated with surgery alone and in patients with a family history of breast cancer suggests a possible association between the two diseases.

When looking at solid tumors, an increased risk of t-AML has been reported in breast cancer patients treated with chemoradiotherapy ± radiotherapy (Table 1). Praga et al. analyzed 9796 breast cancer patients treated in 19 randomized trials (Praga et al., 2005). The cumulative 8-year risk of t-AML showed wide variability between patients treated with standard or high cumulative doses of epirubicin (0.37% vs 4.97%, respectively). In almost 400,000 breast cancer patients, significant risk factors were also younger age at the time of breast cancer diagnosis, advanced stage disease with distal involvement and treatment using radiotherapy (Martin et al., 2009).A large proportion of patients with testicular cancer can be cured by radiochemotherapy, including topoisomerase II inhibitors and cisplatin, but t-MDS/AML represents a major problem with a mean cumulative risk of 1.3 to 4.7% at 5 years (Travis et al., 2000). An increased incidence of AML was found in children with non-testicular germ cell tumors after chemoradiotherapy, with a cumulative incidence in patients treated with combined chemotherapy and radiotherapy. No cases of leukemia were found in patients treated with radiotherapy or surgery only (Schneider et al.,1999).

2.2.3. Hematopoietic stem cell trasplantation

An increased risk of therapy-related myelodysplastic syndrome and t-AML after high-dose therapy and autologous stem-cell transplantation (ASCT) for malignant lymphoma has been described by several studies, reporting a highly variable incidence ranging from 1-3% (Lenz et al., 2004; Howe et al., 2003) to 12% (Micallef et al., 2000). The incidence of therapy-related myeloid neoplasms after SCT is related to the type of conditioning regimens, as patients receiving the combination of TBI and alkylating agents seem to have an especially increased risk, but also to the type of previous chemotherapy, its effects on harvested hematopoietic stem cells and the use of growth factors. The development of t-MN after SCT has been shown to be associated with and preceded by markedly altered telomere dynamics in hematopoietic cells, which may reflect increased clonal proliferation and/or altered telomere regulation in premalignant cells (Chakraborty et al., 2009). In the allogeneic bone marrow or hematopoietic stem cell transplantation setting, donor cell–derived leukemias (DCL) and myelodysplastic neoplasms represent a rare but intriguing form of leukemogenesis. DCL represents a unique form of leukemogenesis in which normal donor cells become transformed into an aggressive leukemia or MDS following engraftment in a foreign host environment (Wang et al., 2011; Sala-Torra et al., 2006).

2.2.4. Auto-immune diseases

The risk of developing therapy-related AML also applies to patients with non-malignant conditions, such as autoimmune diseases treated with cytotoxic and/or immunosuppressive

http://dx.doi.org/10.5772/52459

agents. There is considerable evidence to suggest an increased occurrence of hematologic malignancies in patients with autoimmune diseases compared to the general population, with a further increase in risk after exposure to cytotoxic therapies. Unfortunately, studies have failed to reveal a clear correlation between leukemia development and exposure to individual agents used for the treatment of autoimmune diseases. The association of t-AML and autoimmune diseases was clearly demonstrated in a recent study reporting for an odds ratio of AML OR=1,29 (95% CI, 1.2–1.39) by comparing 13,486 patients aged over 67 years with myeloid malignancies to 160,086 population-based matched controls using the SEER-Medicare database of Hematopoietic Malignancy Risk Traits (SMAHRT). Specifically, AML was associated with rheumatoid arthritis (OR 1.28), systemic lupus erythematosus (OR 1.92), polymyalgia rheumatica (OR 1.73), autoimmune haemolytic anaemia (OR 3.74), systemic vasculitis (OR 6.23), ulcerative colitis (OR 1.72) and pernicious anaemia (OR 1.57) (Anderson et al., 2009). This was confirmed in a recent study by Kristinsson et al. that included 9,219 patients with AML and 42,878 matched controls from population-based central registries in Sweden and reported for a 1.7-fold (95% CI, 1.5–1.9) increased risk of AML (Kristinsson et al., 2011).

In summary, certain inflammatory medical conditions and a personal history of cancer, independent from therapy, are associated with an increased risk of myeloid leukemia. According to the WHO classification, the distinction of t-AMLs from de novo leukemias is solely based on the patient's history but not on the specific biomarkers. Interestingly, it has been observed that 20–30% of acute leukemias, occurring as second malignancy, developed in the absence of previous chemo and/or radiotherapy exposure suggesting that besides the proven leukemogenic mechanisms of chemo and immunosuppressive therapy and ionizing radiations, other factors such as genetics, chronic immune stimulation and environment could favour the onset of multiple neoplastic diseases (Pagano et al., 2001; Johnson et al., 2012). We have to admit that there is insufficient evidence to label leukemias that develop in patients who are exposed to cytotoxic agents as 'therapy-related leukemias'. Further investigation of the underlying mechanisms and defects, including defects in immunity, DNA repair, and apoptosis in these patients are warranted rather than studying only drug mechanisms that lead to leukemogenesis .

3. Risk factors for the development of t-AML

Despite that it has been suggested that chemotherapy (CT) and radiotherapy (RT) are associated with a considerable increase in the risk for the development of t-AML compared to the general population, it still only occurs in a relatively small number of patients. The actuarial risk varies from study to study, but an increase in the risk of AML of 0.25 to 1 % per year has been generally observed. The risk is dose dependent and increases exponentially with age after the age of 40 years, paralleling the risk of primary AML in the general population (Pedersen-Bjergaard J., 2005).

It is important to identify risk factors that may confer susceptibility to the development of the condition, including life style, environmental and occupational, as well as host factors,

such as differences in drug catabolism, membrane transport or inefficient DNA repair that could explain the predisposition to leukemia. In general chemotherapy confers a greater risk while involved field radiation is associated with very little or no increased risk of leukemia. Characteristic features often relate to the type of previous therapy; alkylating agents or RT; drugs binding to the enzyme DNA-topoisomerase, or antimetabolites.

3.1. Host factors

Lichtman (2007) after a review of 463 618 cases of cancer patients treated with chemotherapy and radiotherapy, reported 741 cases of AML/MDS, or less than 1%. These data clearly demonstrate, that after exposure to chemotherapy and/or radiotherapy only a small proportion of patients develop t-AMLs, which supports the idea, that a host predisposition to the leukemogenic potential of chemotherapy and radiotherapy probably exits (Czader & Orazi, 2009). Understanding individual susceptibility factors is important not only to identify patients at risk in order to tailor therapy, but also to clarify the biological processes leading to leukemogenesis (Leone et al.,2007).

3.1.1. Cancer susceptibility conditions

During the last years, a number of factors were identified, that might cause a predisposition to both de novo and t-AML, including several cancer susceptibility syndromes (Knoche et al., 2006). **Neurofibromatosis type 1 (NF1)** results from a mutation in or deletion of the *NF1* gene. The gene product neurofibromin serves as a tumor suppressor; and the decreased production of this protein results in the myriad of clinical features. Children with *NF1* are at increased risk of developing benign and malignant solid tumors as well as hematologic malignancies, including acute myelogenous leukemia. The normal *NF1* allele is frequently deleted in the bone marrow cells from NF1 patients with hematologic malignancies, suggesting a pathogenic role in primary leukemogenesis. The idea that NF1 is essential to regulate the growth of myeloid cells and functions as a tumor suppressor gene raises the possibility that children with NF1 might be susceptible to the development of secondary leukemias. (Maris et al.,1997)

Similarly, **germline p53 mutations** may predispose some children to therapy-related leukemia and myelodysplasia. Several reports described the occurrence of t-AML in single cases but no consistent association has been reported to date (Felix et al., 1996; Talwalkar et al., 2010; reviewed in Sill et al., 2011).

Some observation also suggest that individuals with constitutional genetic variation in the p53 pathway such as certain allelic variants within the *MDM2* and *TP53* genes – both involved in the *TP53* DNA damage response pathway – wereat significantly increased risk for chemotherapy-related AML. Analysis of associations between patients with t-AML and 2 common functional p53-pathway variants, the *MDM2* SNP309 and the *TP53* codon 72 polymorphism revealed that, an interactive effect was detected such that *MDM2* TT *TP53* Arg/Arg double homozygotes, and individuals carrying both a *MDM2* G allele and a *TP53* Pro allele, were at increased risk of t-AML. This interactive effect was observed in patients

previously treated with chemotherapy but not in patients treated with radiotherapy, and in patients with loss of chromosomes 5 and/or 7. In addition, there was a trend toward shorter latency to t-AML in *MDM2* GG versus TT homozygotes in females but not in males, and in younger but not older patients.These data indicate that the *MDM2* and *TP53* variants interact to modulate responses to genotoxic therapy and are determinants of risk for t-AML (Ellis et al., 2008).

The ***RUNX1/AML1* gene** is the most frequent target for chromosomal translocation in leukemia. Besides, point mutations in the *RUNX1* gene are another mode of genetic alteration in development of leukemia. Monoallelic germline mutations in *RUNX1* result in familial platelet disorder predisposed to acute myelogenous leukemia (Osato M., 2004). Among therapy-related myeloid neoplasms after successful treatment for acute promyelocytic leukemia, leukaemia transformation of myeloproliferative neoplasms has been reported to have a strong association with *RUNX1* mutations. The mutations occur in a normal, a receptive, or a disease-committed hematopoietic stem cell (Harada & Harada, 2011).

Recently, an oncogenic germline ***C-RAF*** mutations were described in patients with t-AML. Besides, analysis of blast cells from patients with *C-RAF* germline mutations revealed loss of the tumor and metastasis suppressor *RAF kinase inhibitor protein* (RKIP) as a functional somatic event in carriers of C-RAF germline mutations, which contributes to the development of t-AML (Zebisch et al., 2009).

Over the last years, **genome-wide association studies** were also conducted in the attempt to increase the knowledge of susceptibility factors for t-AML. A recent study of Knight et al., 2009, represents an important step toward the translational goal of identifying persons at risk for t-AML at the time of their original cancer diagnosis so that their initial cancer therapy can be modified to minimize this risk. The major findings were that the effect of genetic factors contributing to cancer risk are potentiated and more readily discernable in t-AML compared with sporadic cancer. Even in a small sample set, this enrichment allowed for the identification and replication of likely t-AML–predisposing genetic variants, each of which may contribute significantly to overall risk. Distinct subsets of patients with t-AML may have distinct inherited susceptibilities toward t-AML (Knight et al., 2009).

A novel concept addresses **epigenetic modifications** as an important factor in conferring disease susceptibility, including global hypomethylation resulting in chromosomal instability and loss of genetic integrity, and promoter specific DNA hypermethylation which leads to silencing of tumor suppressor genes. Recent studies by Voso et al., 2010 demonstared that gene promoter methylation is a common finding in t-MDS/AML and has been associated to a shorter latency period from the treatment of the primary tumor. Among the studied genes, p15 methylation correlated to monosomy/deletion of chromosome 7q, suggesting that it could be a relevant event in alkylating agent-induced leukemogenesis.

DAPK1 was more frequently methylated in t-MDS/AML when compared to de novo MDS and AML (39% vs 15.3% and 24.4%, p=0.0001). Besides, the methylation pattern appeared to be related to the primary tumor, with DAPK1 more frequently methylated in patients with a previous lymphoproliferative disease (75% vs 32%, p=0.006). In patients studied for concur-

rent methylation of several promoters, t-MDS/AML were significantly more frequently hypermethylated in 2 or more promoter regions than de novo MDS or AML suggesting that promoter hypermethylation of genes involved in cell cycle control, apoptosis and DNA repair pathways is a frequent finding in t-MDS/AML and may contribute to secondary leukemogenesis. These studies support the hypothesis that chemotherapy and individual genetic predisposition have a role in t-MDS/AML development, and the identification of specific epigenetic modifications may explain complexity and genomic instability of these diseases and give the basis for targeted-therapy. The significant association with previous malignancy subtypes may underlie a likely susceptibility to methylation of specific targets and a role for constitutional epimutations as predisposing factors for the development of therapy-related myeloid neoplasm. However, how the epigenetic machinery is disrupted after chemo/radiotherapy and during secondary carcinogenesis is still unknown, warranting further studies (Voso et al., 2010; Greco et al., 2010).

3.1.2. Detoxification pathways

Another probable mechanisms that predispose to t-AML could be related to accumulation of reactive species that escape detoxification mechanisms or are produced in excess due to drug metabolizing enzymes polymorphisms, or due to DNA damage which is inefficiently repaired because of defective DNA-repair (Seedhouse et al., 2004).

Drug or xenobiotic metabolizing enzymes play key roles in the detoxification of xenobiotics, as well as of a number of commonly used chemotherapeutics. Besides, drug metabolizing enzymes display a high degree of polymorphism in the general population. The potential role of the polymorphisms of most of these genes in the etiology of primary or t-AML has been suggested (Perentesis, 2001).

One of the most important compounds of CYP system is a *CYP3A* that takes part in the metabolism of various chemotherapeutics, such as epipodophyllotoxins, etoposide and teniposide, as well as cyclophosphamide, ifosphamide, vinblastine, and vindesine. It has been reported that a polymorphism in the 5' promoter region of the *CYP3A4* gene (*CYP3A4*-V) may decrease production of a precursor of the potentially DNA-damaging quinone (Felix et al., 1998), therefore the variant gene showed a protective effect against the development of t-AML (Rund et al., 2005). In contrast, individuals with the *CYP3A4*-wild type genotype are at increased risk for t-AML. Often, polymorphic variants in detoxification enzymes may cooperate in modulating the individual's risk of AML. The absence of polymorphism variants *CYP1A1*2A*, del{GSTT1} and *NQO1*2* is associated with a 18-fold lower risk of t-AML, whereas the presence of only *NQO1*2* or all three polymorphisms enhances the risk of t-AML (Bolufer et al., 2007).

Glutathione S-transferases (GSTs) detoxify potentially mutagenic and DNA-toxic metabolites of several chemotherapeutic agents, such as adriamycin, BCNU, bleomycin, chlorambucil, cisplatin, etoposide, melphalan, mitomycin C, mitoxantrone, vincristine, cyclophosphamide, etc. The variant allele of *GSTP1* gene, with a substitution of isoleucine to valine at amino acid

codon 105, is associated with a decreased activity of the enzyme and is over-represented in t-AML cases compared with de novo AML, particularly among those with prior exposure to known *GSTP1* substrates, but not among patients exposed to radiotherapy alone (Allan et al., 2001).

An increased risk of developing t-AML has been observed in breast cancer patients with a 677T/1298A haplotype in *MTHFR*, the gene encoding methylene tetrahydrofolate reductase involved in methotrexate metabolism, as well as in patients with 677C/1298C haplotype treated for a primary hematopoietic malignancy with a cyclophosphamide-including regimes (Guillem et al., 2007).

3.1.3. DNA repair

Another mechanism implicated into the t-AML development includes defects of the individual DNA-repair machinery which is genetically determined and is believed to be the result of combinations of multiple genes, each of which may display subtle differences in their activities. Double-strand breaks in DNA lead either to cell death or loss of genetic material resulting in chromosomal aberrations. Insufficient repair results in acquisition and persistence of mutations, whereas elevated levels of repair can inhibit the apoptotic pathway and enable a cell with damaged DNA, attempting repair, to misrepair and survive (Leone et al., 2007).

There is accumulating evidence suggesting a role for **mismatch repair (MMR)** in susceptibility to t-AML. MMR is functionally reflected as microsatellite instability which has been reported in a significant number of t-AML patient presentation samples (reviewed in Seedhouse et al, 2007). However, **double strand breaks (DSBs)** in DNA are arguably the most important class of DNA damage because they may lead to either cell death or loss of genetic material, resulting in chromosome aberrations. High levels of DSBs arise following ionising irradiation and chemotherapy drug exposure. Therefore, DSB repair seems to be critical for t-AML susceptibility. The *RAD51* gene plays a key role in DNA-repair process and its variant *RAD51*-G135C is associated with a 2.66-fold increased risk of t-AML compared to a control group (Jawad et al., 2006). If variants of more than one DNA-repair genes are present, for example RAD51-135C and XRCC3-241Met, the risk of t-AML development is even higher (OR 8.11), presumably because of the large genotoxic insult these patients receive after their exposure to radiotherapy or chemotherapy (Seedhouse et al., 2004). Interestingly, it seems that polymorphic variants in DNA-repair and detoxification enzymes may co-operate, thus having a synergistic effect that leads to modulation of the individual's risk of AML.The risk of development of AML is further increased (OR 15.26) in patients in which the burden of DNA damage is increased when a deletion of the GSTM1 gene is present (Seedhouse et al., 2004). Similarly, carriers of both the RAD51-G135C and CYP3A4-A-290G variants are at highest AML risk (Voso et al., 2007). Besides, the genetic interaction between an increased DNA repair capacity in patients with *RAD51*-G135C, associated with suppressed apoptosis, and affected stem cell numbers due to

a *HLX1*-homeobox gene polymorphism, may increase the number of genomes at risk during cancer therapy and results in an increased risk of t-AML up to 9.5-fold (Jawad et al., 2006).

Another possible mechanisms might involve the **base excision repair (BER) pathway, which** corrects individually damaged bases, occuring as the result of endogenous processes, ionising irradiation and exogenous xenobiotic exposure; and the **nucleotide excision repair (NER)** that removes structurally unrelated bulky damage induced by ultra violet radiation, environmental factors and endogenous processes and repairs a significant amount of DNA damage caused by chemotherapeutic agents. A few studies addressed the possible role of polymorphisms of DNA repair genes encoding the X-ray cross-complementing group 1 (XRCC1) protein which plays an important role in excision and ligation of oxidized DNA bases and strand breaks, in cooperation with other enzymes in the base excision repair (BER) pathway, as well as NER polymorphisms, particularly *ERCC2* (XPD) Lys751Gln SNP. Polymorphisms of these genes are associated with decreased DNA repair rates and increased genotoxic damage, measured by single-strand breaks and chromosomal aberrations. It might be speculated that compromised repair activity may lead to accumulation of DNA damage and predispose to secondary cancers and increased treatment-related toxicity to normal tissues. There is a large set of data implying the functional importance of the *XRCC1*-399 polymorphism with the variant Gln allele being associated with a decreased capacity to repair DNA damage and a consequent increased level of DNA damage (reviewed in Seedhouse & Russel, 2007). Evidence has been provided that the variant glutamine allele of XPD Lys751Gln SNP has been associated with an increased risk of t-AML (Kuptsova-Clarkson et al., 2010). Interestingly, Seedhouse et al., 2002 demonstrated that the presence of variant *XRCC1*-399Gln was protective for t-AML hypothesising that when haematopoietic progenitor cells in the bone marrow are damaged by therapy, cells with the *XRCC1*-399Gln allele (reduced BER capacity) are likely to be driven towards apoptosis, whilst those wild type cells are more likely to attempt repair, harbour mutations and initiate clonal disease resulting in t-AML (Seedhouse et al., 2002).

3.2. Previous therapy

By definition t-AMLs occur as late complications of cytotoxic chemotherapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder (Vardiman et al., 2008). Chemotherapy and ionizing radiation cause extensive DNA damage and affect unfortunately not only neoplastic but also normal cells. Presumably if genes controlling growth and differentiation of haematopoietic stem cells are affected, a neoplastic myeloid clone may arise. Further, repeated therapies may facilitate the selection of such a clone due to the inevitable immunosupression.

Mechanism of action	Agent	References
Alkylating agents	Busulfan	Dastugue et al., 1990
	Carboplatin	Miyata et al., 1996
	Carmustine	Perry et al., 1998

Mechanism of action	Agent	References
	Chlorambucil	Rosenthal et al., 1996
	Cisplatin	Samanta et al., 2009
	Cyclophosphamide	Au et al., 2003
	Dacarbazine	Collins et al., 2009
	Dihydroxybusulfan	Pedersen-Bjergaard et al.,1980
	Lomustine	Perry et al., 1998
	Mechlorethamine	Metayer et al., 2003
	Melphalan	Kyle et al., 1070; Yang et al., 2012
	Mitolactol	Bennett et al., 1994
	Mitomycin C	Nakamori et al., 2003
	Procarbazine	Travis et al., 1994
	Semustine	Boice et al., 1983
	Temozolomide	Noronha et al., 2006
Topoisomerase II inhibitors	4-Epidoxorubicin	Riggi et al., 1993
	Bimolane	Xue et al., 1997
	Dactinomycin	Scaradavou et al., 1995
	Daunorubicin	Blanco et al., 2001
	Doxorubicin	Yonal et al., 2012
	Etoposide	Haupt et al., 1994
	Mitoxantrone	Colovic et al., 2012
	Razoxane	Bhavnani et al., 1994
	Teniposide	Ezoe et al. 2012
Antimetabolites	5-fluorouracil	Turker et al., 1999
	Fludarabine	Smith et al., 2011
	6-Mercaptopurine	Bo et al., 1999
	Methotrexate	Kolte et al., 2001
Antimicrotubule agents	Docetaxel	Griesinger et al., 2004
	Paclitaxel	See et al., 2006
	Vinblastine - leukemogenic effects were not confirmed	Carli et al., 2000
	Vincristine - leukemogenic effects were not confirmed	Carli et al. 2000
Growth factors	Granulocyte colony-stimulating factor	Relling et al., 2003
	Granulocyte-macrophage colony-stimulating factor	Hershman et al., 2007
Immunomodulators	Azathioprine	Kwong et al.,2010

Table 2. Cytotoxic agents implicated in t-AML.

Although increased risk of t-AML has been observed after chemotherapy or radiotherapy alone or in combination, chemotherapy generally confers greater risk. Radiation alone is rarely associated with increased risk of t-AML. However, cytotoxic drugs are often given in complex schedules and sometimes in combination with radiotherapy, making it difficult to assess the tumorigenic role of each drug. The most common cytotoxic drugs commonly implicated are listed in the Table 2.

3.2.1. Alkylating agents

Alkylaing agents were the first chemotherapeutics to be associated with secondary leukaemia development after successful treatment of other solid or haematopoietic neoplasms (Kyle et al., 1970; Smit & Meyler, 1970). The mechanisms of DNA damage include either methylation or DNA inter-stand crosslinking formation. Monofunctional alkylating agents (incl. dacarbasine, procarbasine, temozolomide) have one reactive moiety and generally induce base lesions by transferring alkyl groups (-CH_3 or CH_2-CH_3) to oxygen or nitrogen atoms of DNA bases, resulting in highly mutagenic DNA base lesions (reviewed in Drablos et al., 2004). In contrast, bifunctional alkylating agents (incl. melphalan, cylophosphamide, chlorambucil) have two reactive sites and in addition to DNA base lesions, intra- and interstrand crosslinks can be formed by attacking two bases within the same or on opposing DNA strands which furtheron could result in translocations, inversions, insertions and loss of heterozygosity (reviewed in Helleday et al., 2008).

The latency between treatment and t-MN is generally long, between 5 and 7 years, and overt leukemia is frequently preceeded by a dysplastic phase. These cases are generally characterized by loss or deletion of chromosome 5 and/or 7 [-5/del(5q), -7/del(7q)]. In the University of Chicago's series of 386 patients with t-MDS/t-AML, 79 patients (20%) had abnormalities of chromosome 5, 95 patients (25%) had abnormalities of chromosome 7, and 85 patients (22%) had abnormalities of both chromosomes 5 and 7. t-MDS/t-AML with a -5/del(5q) is associated with a complex karyotype, characterized by trisomy 8, as well as loss of 12p, 13q, 16q22, 17p (*TP53* locus), chromosome 18, and 20q. In addition, this subtype of t-AML is characterized by a unique expression profile (higher expression of genes) involved in cell cycle control (*CCNA2*, *CCNE2*, *CDC2*), checkpoints (*BUB1*), or growth (*MYC*), loss of expression of *IRF8*, and overexpression of *FHL2*. Haploinsufficiency of the *RPS14*, *EGR1*, *APC*, *NPM1*, and *CTNNA1* genes on 5q has been implicated in the pathogenesis of MDS/AML (Qian et al., 2010). Cases with−7/7q−, but normal chromosome 5 often have methylation of the *CDKN4B* gene promoter and somatic mutations of the *RUNX1* gene (Christiansen et al., 2004). Thus, two major patterns of t-AML after alkylating agents have been identified (Pedersen-Bjergaard et al., 2006).

3.2.2. Topoisomerase II inhibitors

Commonly used topoisomerase inhibitors bind to the enzyme/DNA complex at the strand cleavage stage of the topoisomerase reaction, interacting with topoisomerase I (topotecan) or II(doxorubicin, epipodophyllotoxin, e.g. etoposide and teniposide). Topoisomerase II inhibitors block the enzymatic reaction through religation and enzyme release, leaving the DNA

with a permanent strand break. Chromosomal breakpoints have been found to be preferential sites of topoisomerase II cleavage, which are believed to be repaired by the nonhomologous end-joining DNA repair pathway to generate chimaeric oncoproteins that underlie the resultant leukaemias (reviewed in Joannides & Grimwade, 2010).

T-AMLs occur after a shorter latency time, ranging between 1 and 3 years from the primary treatment, usually arising without a previous dysplastic phase. Several factors, such as the schedule and the concurrent use of asparaginase, dexrazoxane or G-CSF, are considered very important in determining the relative risk. Exposure to topoisomerase II inhibitors is predominantly associated with t-AML characterized by reciprocal translocations with as many as 40 different partner genes, such as t(9;11), t(19;11) or t(4;11) in 80% of the cases, as well as with internal duplications, deletions, and inversions translocations of the *MLL* gene on chromosome band 11q23 Other less frequent genetic alterations are t(8;21), t(3;21), t(16;21), t(17;21), inv(16), t(8;16), t(9;22), t(15;17) (Cowell et al., 2012; Salas et al., 2011, Yin et al., 2005; Felix, 1998).

3.2.3. Antimetabolites

Antimetabolites (e.g. azathioprine, 6-thioguanine, fludarabine) share structural similarities with nucleotides, and can be incorporated into DNA or RNA, thereby interfering with replication and causing inhibition of cell proliferation. Once placed in the newly synthesized DNA strand, metabolites are prone to methylation and formation of the highly mutagenic base lesions that closely resemble the induced by alkylating agents. Cell cycle arrest and cell death after treatment are triggered by the DNA MMR machinery. However, MMR-deficient cells can tolerate methylated lesions, potentially forming a leukaemic clone (Offman et al., 2004). In line with the cytogenetic aberrations found with alkylating agents, patients with t-AML after antimetabolites treatment frequently harbour partial or complete loss of chromosomes 5 and 7 (Morrison et al., 2002; Smith et al., 2011).

3.2.4. Granulocyte-colony stimulating factor (G-CSF)

Since some of G-CSF effects include stimulation of the proliferation of granulocytic progenitors and premature release of neutrophils from the bone marrow enhancing their capacity for phagocytosis, ROS (reactive oxygen species) generation and bacterial cell killing, two mechanisms have been implicated in the G-CSF-mediated promotion of therapy-related myeloid neoplasms (Beekman & Touw, 2010). First, G-CSF-induced production and release of ROS by bone marrow neutrophils may result in increased DNA damage and mutation rates in Human hematopoietic stem and progenitor cells (Touw & Bontenbal, 2007). Second, repeated application of G-CSF results in a continuous leaving of these cells from their protective bone marrow niche, which may render them more susceptible to genotoxic stress (Trumpp et al., 2010). In an attempt to evaluate the risk of acute myeloid leukemia or myelodysplastic syndrome in patients receiving chemotherapy with or without G-CSF, Lyman et al., 2010 systematically reviewed 25 randomized controlled trials and identified 6058 and 6746 patients were randomly assigned to receive chemotherapy with and without initial G-CSF support, respectively. An absolute risk of 0.43% was determined, however, the adminis-

tration of G-CSF showed benefits for a substantial proportion of patients and outweighs the increased risk of secondary leukemias.

3.2.5. Ionizing radiation

The risk of leukemia following radiation is considerably smaller than after chemotherapy, with a relative peak at the 5th to 9th year after radiotherapy exposure showing a slow decline afterwards. The underlying mechanisms refer to the formation of reactive oxygen species through radiolysis of water molecules resulting from the exposure of cells to ionizing radiation, which are highly reactive and capable of oxidizing or deaminating DNA bases and increasing the frequency of DNA double strand breaks (Rassool et al., 2007), on one hand, or can also directly induce strand breaks by disruption of the sugar phosphate backbone of DNA, potentially leading to the formation of large scale chromosomal rearrangements (Klymenko et al., 2005). The radiation-related leukemia risk depends on the dose given to the active bone marrow, the dose rate, and the extent of exposed marrow (Travis L., 2006). Due to cell killing at higher doses the risk of t-AML is considerably larger at low doses: patients in whom high radiation doses to limited fields have been given are associated with little or no increased risk of leukemia (UNSCEAR 2000 Report), while exposure of extended fields of radiotherapy as well as low-dose total body irradiation may result in considerably higher risks (Travis et al., 1996; Travis et al., 2000) of leukemia.

4. Molecular pathogenesis

It has been suggested, that t-AML are a direct consequence of mutational events induced by chemotherapy, radiation therapy, immunosuppressive therapy, or a combination of these modalities (Godley & Larson, 2008). Similarly to de novo AML, t-AMLs are complex genetic diseases, requiring cooperating mutations in interacting pathways for disease initiation and progression. Establishing a leukaemic phenotype requires acquisition of crucial genetic aberrations, such as point mutations, fusion genes formation or gene rearrangements, deletion or inactivation of tumor-suppressor genes, or changes in the expression of critical oncogenes or growth factor receptor genes (Larson, 2004). Most probably, multiple events are involved in which DNA damage from exposure to genotoxic stress leads to the secondary abnormalities that cause t-AML (Pedersen-Bjergaard, 2001). A major difference between t-AML and de novo AML is that high doses of mutagenic chemo-/radiotherapy impact on the DNA of haematopoietic stem and precursor cells in the socondary myeloid neoplasms. In contrast, chronic exposure to low doses of occupational/environmental agents over extended periods of time may be operational in the development of high-risk de novo MDS/AML (Sill et al., 2011).

However, these differences are not apparent in all cases and there is a clinical and biological overlap between t-AML and high-risk de novo myelodysplastic syndromes and acute myeloid leukaemia suggesting similar mechanisms of leukaemogenesis. Recently, similarities in therapy-related and elderly acute myeloid leukemia were found in terms of the similar clinical and molecular aspects and unfavorable prognosis. In older individuals prolonged expo-

http://dx.doi.org/10.5772/52459

sure to environmental carcinogens may be the basis for these similarities (D'Alò et al., 2011). On the other hand, a recently published study reported that AML diagnosed in the past decade in patients after receiving radiotherapy alone differ from therapy-related myeloid neoplasms occurring after cytotoxic chemotherapy/combined-modality therapy and share genetic features and clinical behavior with de novo AML/MDS, suggesting that post-radiotherapy MDS/AML may not represent a direct consequence of radiation toxicity (Nardi et al., 2012). Therefore, other factors might be involved such as genetic variants conferring predisposition to the primary malignacy that may also be of relevance for therapy-related leukaemogenesis and account for subtle biologic differences between t-MNs and high-risk de novo MDS/AML (Sill et al., 2011). Besides, the nature of the causative agent has an important bearing upon the characteristics, biology, time to onset and prognosis of the resultant leukaemia (Joannides & Grimwade, 2010).

Various pathogenetic mechanisms have been elucidated so far and different genetic pathways for the multistep development of t-MDS/t-AML have been proposed, in which particular mechanisms of DNA damage that lead either to chromosomal deletions, balanced translocations or induction of defective DNA-mismatch repair could promote survival of misrepaired cells giving rise to the leukemic clone (Leone at al., 2007). Multiple tumor suppressor genes or oncogenes may need to be mutated to ultimately transform a cell resulting in impaired differentiation of hematopoietic cells and/or in proliferative and survival advantage. Different molecular pathways may cooperate in the genesis of leukemia and at least 8 alternative genetic pathways have been defined based on characteristic recurrent chromosome abnormalities(Pedersen-Bjergaard et al., 2007).

Interestingly, analysis of gene expression in CD34+ cells from patients who developed t-MDS/AML after autologous hematopoietic cell transplantation revealed altered gene expression related to mitochondrial function, metabolism, and hematopoietic regulation and the genetic programs associated with t-MDS/AML are perturbed long before disease onset (Li et al., 2011). Similarly, the gene expression profiles in diagnostic acute lymphoblastic leukemic cells from children treated on protocols that included leukemogenic agents, revealed a signature of 68 probes, corresponding to 63 genes, that was significantly related to risk of t-AML. The distinguishing genes included transcription-related oncogenes (*v-Myb*, *Pax-5*), cyclins (*CCNG1*, *CCNG2* and *CCND1*) and histone *HIST1H4C*. Common transcription factor recognition elements among similarly up- or downregulated genes included several involved in hematopoietic differentiation or leukemogenesis (*MAZ*, *PU.1*, *ARNT*). This approach has identified several genes whose expression distinguishes patients at risk of t-AML, and suggests targets for assessing germline predisposition to leukemogenesis (Bogni et al., 2006).

The comparison of samples from t-AML and de novo AML patients using high resolution array CGH revealed more copy number abnormalities (CNA) in t-AML than in de novo AML cases: 104 CNAs with 63 losses and 41 gains (mean number 3.46 per case) in t-AML, while in de novo-AML, 69 CNAs with 32 losses and 37 gains (mean number of 1.9 per case). The authors suggested that CNA can be classified into several categories: abnormalities

common to all AML; those more frequently found in t-AML and those specifically found in de novo AML (Itzhar et al., 2011).

Recently, a growing amount of data suggests that DNA methylation abnormalities may contribute to a multistep secondary leukemogenesis. Two distinct alterations of normal DNA methylation patterns may occur in cancer: (i) a global hypomethylation resulting in chromosomal instability and loss of genetic integrity, and (ii) promoter specific DNA hypermethylation which leads to silencing of tumor suppressor genes. Cytotoxic drugs and radiation have been shown to affect tissue DNA methylation profile. Radiation is able to induce a stable DNA hypomethylation in both target and bystander tissues. Gene promoter methylation is a common finding in t-MDS/AML and has been associated to a shorter latency period from the treatment of the primary tumor. Among the studied genes, *p15* methylation correlated to monosomy/deletion of chromosome 7q, suggesting that it could be a relevant event in alkylating agent-induced leukemogenesis. Besides, a frequent methylation of *DAPK* in the t-MDS/AML group was observed, especially in patients with a previous lymphoproliferative disease. In patients studied for concurrent methylation of several promoters, t-MDS/AML were significantly more frequently hypermethylated in 2 or more promoter regions than de novo MDS or AML suggesting that promoter hypermethylation of genes involved in cell cycle control, apoptosis and DNA repair pathways is a frequent finding in t-MDS/AML and may contribute to secondary leukemogenesis. However, how the epigenetic machinery is disrupted after chemo/radiotherapy and during secondary carcinogenesis is still unknown (Voso et al., 2010).

5. Clinical features

Similarly to de novo AML, therapy-related AMLs comprise an extremely heterogeneous group of biologically different hematologic malignancies and their clinical presentation varies in a significant degree from cases to case, depending on applied chemo- and or radiotherapy for the primary disorder as well as on other factors.

As expected, the most frequent complaints at the presentation of patients with t-AMLs include: fatigue, weakness, and occasionally fever, bleeding complications caused by thrombocytopenia, anemia, and leukopenia. Features that are fairly common in de novo acute leukemia, such as hepatomegaly, splenomegaly, lymphadenopathy, gingival hyperplasia, skin rash, or neurological complications, are notably absent from the presentations of patients with t-MDS/t-AML. Bone marrow biopsies typically reveal hypercellularity with some degree of marrow fibrosis, although hypocellular and even aplastic marrows can be seen (Godley & Le Beau, 2007).

Morphologically, t-AML can present in the broad spectrum of myeloid leukemias. Mostly in patients after previous therapy with alkylating agents multilineage dysplasia can be observed. However, dysplasia can be seen in some patients with balanced translocations as well. Dysgranulopoiesis includes hypogranular neutrophils, with hypo- or hyperlobulated nuclei, nuclear excrescences, and pseudo-Pelger-Huet nuclei. Red cell morphology in most

cases is characterised by macrocytosis and poikilocytosis, periodic acid-Schiff-positive normoblasts, dyserythropoiesis with megaloblastoid changes, erythroid hyperplasia, ringed sideroblasts, nuclear budding, karyorrhexis, binuclearity, and nuclear bridging. Megakaryocyte dysplasia within the bone marrow includes micromegakaryocytes, abnormal nuclear spacings, mononuclear forms, giant compound granules, and hypogranular cytoplasm. Cases of therapy-related myeloid neoplasms related to treatment with topoisomerase II inhibitors typically present as overt acute myeloid leukemia without a myelodysplastic prephase. Morphologic features are not unique in therapy-related cases. Although monocytic and monoblastic differentiation is often present, the appearance may be that of de novo cases, including those with recurrent cytogenetic abnormalities (Godley & Le Beau, 2007; Vardiman et al., 2008).

Immunophenotypic studies are not used to distinguish t-AML from de novo cases but rather to clarify abnormal populations, reflecting the heterogeinety of the underlying morphology. The phenotype findings are similar to their de novo counterparts. The myeloblasts are characteristically CD34-positive and express pan-myeloid markers (CD13, CD33) and flow cytometry may be helpful in assessing the proportion of myeloid blasts, as well as aberrant antigenic expression, such as CD7, CD56, CD19, etc. Immunophenotypic maturation patterns of the myeloid and erythroid lineages may also be evaluated. The maturing myeloid cells may show abnormal patterns of antigen expression and/or light scatter properties. However, the relevance of such findings is similar to that in de novo cases (Wood B., 2007; Vardiman et al., 2008).

Clinical and laboratory features of patients with t-AML with recurrent genetic abnormalities have been of particular interest. In some studies, hematologic characteristics of patients with t-AML with t(8;21) and inv(16), are identical to those of de novo AML with the same karyotypes (Quesnel et al., 1993). Simmilarly, according to Duffield et al., 2012, t-APL and de novo APL had abnormal promyelocytes with similar morphologic and immunophenotypic features, comparable cytogenetic findings, and comparable rates of FMS-like tyrosine kinase mutations (Duffield et al., 2012). Interestingly, compared with patients with t-APL, those with de novo APL had a greater median body mass index-BMI (31.33 vs. 28.48), incidence of obesity (60.4% vs. 27.3%), and history of hyperlipidemia (45.3% vs. 18.2%), suggesting that abnormalities in lipid homeostasis may in some way be of pathogenic importance in de novo APL (Elliott et al., 2012). t-AML-t(8;21) shares many features with de novo AML-t(8;21)(q22;q22), however patients with t-AML-t(8;21) are older and had a lower WBC count, substantial morphologic dysplasia, Auer rods are detected only certain patients, an increase in eosinophils is uncommon (Gustafson et al., 2009). The detection of morphologic features characteristic of t(8;21) with associated multilineage dysplasia is fairly unique to t(8;21) t-AML/MDS (Arber et al., 2002). Despite that, some studies reported that t-AML/MDS with t(8;21) may have a high frequency of expression of CD19 and CD34 (Arber et al., 2002), this was not confirmed by others (Gustafson et al., 2009).

Rearrangements involving the *MLL* gene on chromosome band 11q23 are a hallmark of therapy-related acute myeloid leukemias following treatment with topoisomerase II poisons (Libura et al., 2005). French-American-British (FAB) subtype distribution of cases with

11q23/*MLL* rearrangement does not differ between de novo AML and t-AML (Schoch et al., 2003). In adults, patients with t-AML and t(9;11)(p21-22;q23) are more likely to be women and older, without other statistically significant differences with regard to clinical features; immunophenotype; morphologic, cytogenetic, and molecular genetic features; or miRNA expression, compared to de novo AML cases (Chandra et al., 2010). Pediatric patients with t(9;11) positive secondary AML are older at diagnosis, have higher hemoglobin levels, and central nervous system leukemia or hepatosplenomegaly is less frequent. Whereas the t(9;11)(p21;q23) occurred exclusively in the FAB M5 subtype in de novo AML, the FAB M0 and M4 subtypes were also represented in secondary cases (Sandoval et al., 1992).

Chromosome/ Molecular Aabnormality	GIMEMA 2001 n=127	**G-A AML SG 2011 n=200**	Serbia 2012 n=42	Our data 2012 n=26	De novo AML, 2011 n= 2653
Age – mean (range) years	58 (21-87)	57.8 (18.6-79.4)	56.07 (23-84)	53.5 (22-83)	53.2 (16.2-85)
Male %/female %	44/56	32/68	29/71	46/54	53/47
Latency median (range) months	52 (2-379)	48.5 (4-530)	54.62 (6-243)	48 (3-216)	NA
WBC – mean x10^9/L	6.7	7.4	27.2	24.4	12.5
CR rate %	55	63	23.8	42	67
Median OS months	7	12	5.94	6	20
Reference	Pagano et al, 2001	Kayser et al, 2011	Suvajdžić et al, 2012	Balatzenko et al., 2012	Kayser et al, 2011

Table 3. Major clinical data in t-AML patients' cohorts.

The analysis of 179 t-AML patients from the GIMEMA Archive of Adult Acute Leukaemia, including 41 treated with surgery only, allowed for the distinction of some differences compared to de novo AML cases. The median age of t-AML was significantly higher than that of other AML (63 years vs. 57 years), the number of men was significantly lower than the number of women [4.8% vs. 7.4%) most probably due to the high incidence in breast cancer patients; as was the number of patients aged <65 years [5.3% vs. 7.5%]. Interestingly, an increased incidence of cancer was observed among first-degree relatives of patients with AML occurring after a primary malignancy [36.9% vs. 27.2% in de novo AML]. Prevalent types of primary malignancies were breast cancer, lymphoma and Hodgkin's disease (Pagano et al., 2001). Higher WBC count and females predominance in t-AML had also been observed by others (Schoch et al., 2004).

http://dx.doi.org/10.5772/52459

6. Genetic and molecular features

It is widely accepted, that the spectrum of chromosome aberrations is comparable in t-AML and de novo AML, however the frequencies of distinct cytogenetic categories is different depending on the characteristics of the analyzed patient cohort (reviewed in Schoch et al., 2004). Two are the most striking features of t-AML: the extremely high frequency of abnormal clonal karyotype up to 75%-96% compared to 50%-59% in de novo AML (Schoch et al., 2004; Godley & Larson, 2008; Grimwade et al., 2010; Mauritzson et al., 2002); and a clear predominance of unfavorable cytogenetics, such as deletion or loss of chromosomes 5 and/or 7 or a complex karyotype (Godley & Larson, 2008). However, the frequency and the spectrum of abnormal karyotypes varies depending on the nature of the applied antecedent anti-neoplastic therapy (Rund et al., 2004).

Unbalanced chromosome aberrations such as abnormalities of chromosomes 5 and/or 7 account for 76% of the cases with an abnormal karyotype.Complex karyotypes are seen in 26.9% of t-AML as compared to 11.30% of de novo AML (Schoch et al., 2004). Recurring balanced rearrangements account for 11% of cases (Larson & Le Beau, 2005), with a specific over-presentation of 11q23 abnormalities – 12.9% vs. 3.7% in de novo AML (Schoch et al., 2004). Comparative data on chromosome/molecular aberrations in t-AML and de novo AML are presented in Table 4.

6.1. Unbalanced chromosome aberrations

Generally, t-AMLs with unbalanced chromosome abnormalities are developed after exposure to alkylating agents and/or ionizing radiation. This group is considered as a biologically distinct form and the most frequent type of t-AML accounting for approximately 75% of cases. The disease usually follows a long period of latency generally occuring 5–10 years after the drug exposure and is characterized frequently by a preleukemic phase and tri-lineage dysplasia. Typical cytogenetical aberrations comprise loss or deletion of chromosome 5 and/or 7 [-5/del(5q), -7/del(7q)]. Frequently, abnormalities of chromosome 5 are part of a complex karyotype, that additionally includes trisomy 8, as well as loss of 12p, 13q, 16q22, 17p (*TP53* locus), chromosome 18, and 20q (Qian et al., 2010).

The complex and hypodiploid karyotypes with unbalanced chromosome changes results in multiple severe molecular abnormalities with a gene-dosage effect for some of the genes that depend on the nature of the primary chromosome aberration. The loss of the coding regions for tumor suppressor genes from hematopoietic progenitor cells is a particularly unfavorable event, since the remaining allele becomes susceptible to inactivating mutations leading to the leukemic transformation (Leone et al., 2001; Joannides & Grimwade, 2011).

Interestingly, significant proportion of older patients are diagnosed with leukaemia with no antecedent history of exposure, and some of these cases show a remarkably similar phenotype to classic therapy-related leukaemia (D'Alò et al., 2011). The specific cytogenetic abnormalities common to MDS, alkylating-agent-related AML and poor-prognosis AML [3q-, -5/5q-, -7/7q-, +8, +9, 11q-, 12p-, -18, -19, 20q-, +21, t(1;7), t(2;11)], probably reflect a common

pathogenesis distinct from that of other de novo AMLs. Possibly, tumour suppressor genes are implicated and genomic instability may be a cause of multiple unbalanced chromosomal translocations or deletions. Typically, these patients are either elderly or have a history of exposure to alkylating agents or environmental exposure 5-7 years prior to diagnosis (Dann & Rowe, 2001).

Chromosome/Molecular Aabnormality	De novo AML	Therapy-related AML
BRAF	1.5%	6%
CEBPA mutations	7% - 15%	0 – 6%
c-KIT mutations	2% - 5%	1% - 4%
DNMT3A mutations	18% - 22%	16%
*FLT3*internal tandem duplications	22% - 35%	7% - 12%
FLT3 – tyrosine kinase domain mutations	5% - 8%	2% - 2.5%
IDH1/IDH2 mutations	17% - 33%	3% -12%
Inv(16)/t(16;16) / *CBFβ-MYH11*	4% - 6%	1% - 8%
Inv(3)/t(3;3) / EVI1	1% - 2%	0.2% - 1%
JAK2 mutations	Rare	Rare
MLL partial tandem duplications	6%	2% - 4%
NPM1 mutations	19% - 35%	12% - 16%
NRAS mutations	6% - 10%	11% - 12%
PTPN11 mutations	3% - 5%	4.%
RUNX1 mutations	5% - 10%	4% - 9%
t(15;17) / *PML-RARα*	4% - 11%	2% - 3%
t(8;21) / *RUNX1-ETO*	5% - 9%	2% - 5%
t(9;11) / *MLLT3-MLL*	1% - 2%	6% - 11%
t(v;11)(v;q23) / *MLL* rearrangements	2% - 4%	4% - 12%
TET2 mutations	8% - 13%	9%
TP53 mutations	10-15%	18% - 25%
WT1 mutations	4% - 7%	17%

References: Abbas et al., 2010; Ahmad et al., 2009; Bacher et al., 2011; Bacher et al., 2007; Christiansen et al., 2005; Christiansen et al., 2004; Christiansen et al.,2007; Fried et al., 2012; Gaidzik et al., 2011; Green et al., 2010; Kayser et al., 2011; Kosmider et al., 2011; Lee et al., 2004; Lin et al., 2005; Marcucci et al., 2010; Mauritzson et al., 2002; Paschka et al., 2010; Pedersen-Bjergaard et al., 2008; Preudhomme et al., 2002; Shen et al., 2011; Takahashi et al., 2000; Thiede et al., 2002; Westman et al., 2011.

Table 4. Chromosome and molecular abnormalities in t-AML compared to de novo AML.

The critical genetic consequences of unbalanced chromosome aberrations in MDS and AML have remained unknown (Pedersen-Bjergaard et al., 2007). The genetic consequences of a deletion may be a reduction in the level of one or more critical gene products (haploinsufficiency), or complete loss of function. The latter model, known as the "two-hit model", predicts that loss of function of both alleles of the target gene would occur, in one instance through a detectable chromosomal loss or deletion and, in the other, as a result of a subtle inactivating mutation, or other mechanisms, such as transcriptional silencing. However, the respective genes on the "intact copy" seem to be not affected, since no submicroscopic deletions or mutations of the remaining allele in any of the genes within the commonly deleted segment (CDS) were detected (reviewed in Le Beau & Olney, 2009). Therefore, most probably loss of only a single copy of a relevant gene (haploinsufficiency) perturbs cell fate. Deletions of putative tumor suppressor genes at chromosomes 5q and 7q are believed to underlie the molecular pathogenesis of alkylating agent- related leukemias. Since similar aberrations occur in de novo MDS/AML, knowledge on potential regions of involvement at chromosomes 5q and 7q derives from de novo and treatment-related cases, but the specific genes in these regions that are important in leukemia pathogenesis continue to remain elusive (Jerez et al., 2011).

On chromosome 5q, two CDSs were identified in 5q31.2 (de novo and t-MDS/t-AML) and 5q33.1 (in 5q− syndrome). The 970 kb CDS within 5q31.2 comprises 20 genes that encoded proteins that take part in regulation of mitosis and G2 checkpoint, transcriptional control, and translational regulation. The second 1.5 Mb CDS is located within 5q33.1, distal to the CDS in 5q31.2 and contains 40 genes, 33 of which are expressed within the CD34+ hematopoietic stem/progenitor cell compartment cells and, therefore, represent candidate genes (Boultwood et al., 2002).The genes that might be involved in leukemogenesis due to gene dosage effect include *RPS14*, *EGR1*, *NPM1*, *APC*, and *CTNNA1* (reviewed in Qian et al., 2010).

Monosomy 7 and del(7q) occur in a variety of clinical contexts including de novo MDS and AML, leukemias associated with a constitutional predisposition, and therapy-related MDS or AML (Luna-Fineman et al., 1995). Several regions with allelic loss were identified in patients with 7q deletions, including entire regions from chromosome 7q22 to 7q31, 7q32-7q35, etc. (Kratz et al., 2001; Le Beau et al., 1996; Dohner et al.,1998). Besides, case analysis of allelic loss at 7q31 and 7q22 loci revealed retention of sequences between these loci or submicroscopic allele imbalance for a different distal locus, suggesting that multiple distinct critical chromosme7q genes are involved in MDS and AML.

Critical genes affected by monosomy 7 and del(7q) are still unknown. Several candidate genes have been suggested as involved in leukemogenesis. *hDMP1* (cyclin D-binding Myb-like protein) gene, that negatively regulates cell proliferation is considered as possible as a tumor suppressor in acute leukemias with deletions of the long arm of chromosome 7 (Bodner et al., 1999). *MLL5* is a candidate tumor suppressor gene located within a 2.5-Mb interval of chromosome band 7q22, that seems to be a key regulator of normal hematopoiesis and which is frequently deleted in human myeloid malignancies. Since no inactivating mutations and decreased *MLL5* mRNA expression were detected, the most probable mechanism

of gene inactivation is haploinsufficiency (Heuser et al., 2009; Zhang et al., 2009; Emerling et al., 2002).

PIK3CG, which encodes the catalytic subunit p110 gamma of phosphoinositide 3-OH-kinase-gamma (PI3K gamma), has been assigned to the same frequently deleted in myeloid malignancies chromosome band 7q22. Although that missense variations affecting residue 859 in the N-terminal catalytic domain of the protein were found, this fact probably represents a polymorphism and it is unlikely that the gene acts as a recessive TSG in myeloid leukemias with monosomy 7 (Kratz et al., 2002).

Deletions of chromosome band 17p13 or loss of a whole chromosome 17 harboring the *p53* gene were shown to be associated with point mutations of *p53*. Patients with *p53* mutations characteristically present complex karyotypes and complicated chromosome rearrangements with duplication or amplification of chromosome bands 11q23 and 21q22 encompassing the *MLL* and the *AML1* genes, resulting in "sandwich-like" marker chromosomes made of material from at least three different chromosomes.

Application of multicolor fluorescence in situ hybridization (M-FISH) allows better identification of chromosome abnormalities compared to G-banding. A clustering of breakpoints was observed in the centromeric or pericentromeric region of chromosomes 1, 5, 7, 13, 17, 21, and 22 in almost 50% of patients with t-MDS and t-AML and an abnormal karyotype. In most of the patients with chromosome derivatives containing material from 3 or more chromosomes or having "sandwich-like" chromosomes, those made up of several small interchanging layers of material from two chromosomes, showed mutations of *TP53* (Andersen et al., 2005).

In some patients treated with alkylating agents an amplification or duplication of *AML1* gene (21q22) or *MLL* gene (11q23) can be found. Generally, no point mutations in *AML1* gene or *MLL* gene rearrangements were seen in these cases. Interestingly, almost all these patients presented with acquired point mutations of the *TP53* gene, which supports the pivotal role of the impaired *TP53* function in the development of gene amplification or duplication in t-MDS and t-AML (Andersen MK, et al.,2001; Andersen MK, et al. 2005).

6.2. Balanced chromosome aberrations

Balanced chromosome translocations and inversions have been found in 10.6% of t-AML. These types of aberrations are observed most commonly in patients treated with agents targeting topoisomerase II. Other typical features of t-AML with balances chromosome abnormalities comprise presentation of the disease as an overt leukemia without a myelodysplastic phase and a short latency period (6–36 months). The formation of these chromosome abnormalities is considered as a result of multiple DNA strand breaks following the topoisomerase II inhibitors. Generally, chromosomal breakpoints have been found to be preferential sites of topoisomerase II cleavage that seems to be repaired by the nonhomologous end-joining DNA repair pathway to generate chimaeric oncoproteins that underlie the resultant leukaemias (Joannides & Grimwade, 2010).

Most often, chromosome translocations involve chromosome bands 11q23 or 21q22 with rearrangement of the *MLL* and the *AML1* genes, but also less frequently other balanced rearrangements such as the inv(16)(p13q22), and the t(15;17)(q22;q11) (Dissing et al., 1998; Andersen MK et al.,1998), etc. Translocations are often present as the sole abnormality.

It seems, that an association between the nature of the applied drug and the type of translocation exists, since translocations involving 11q23 are more frequent after treatment with epipodophyllotoxins, whereas translocations affecting 21q22, inv(16), and t(15;17) are more common after anthracyclines (Andersen et al., 1998). Other less common, recurrent, balanced cytogenetic abnormalities occurring in myeloid neoplasms associated with previous therapy include 3q21q26, 11p15, t(9;22)(q34;q11), 12p13, and t(8;16)(p11;p13) (Czader et al., 2009).

Recently, translocations involving the *NUP98* gene on chromosome 11p15.5 have been cloned from patients with hematological malignancies. To date, at least 8 different chromosomal rearrangements involving *NUP98* have been identified. The resultant chimeric transcripts encode fusion proteins that juxtapose the N-terminal GLFG repeats of *NUP98* to the C-terminus of the partner gene. Of note, several of these translocations have been found in patients with t-AML, suggesting that genotoxic chemotherapeutic agents may play an important role in generating chromosomal rearrangements involving *NUP98* (Lam & Aplan, 2001).

Generally, the recurrent balanced chromosome aberrations lead to the formation of fusion genes, with the participation of hematopoietic transcription factors genes, that encode himeric oncoproteins playing a crtical role in leukemogenesis.

6.2.1. Translocations involving chromosome 11q23/ MLL gene

MLL encodes a histone methyltransferase that play a key role in the regulation of gene expression. In leukemia, this function is subverted due to replacement of the C-terminal functional domains of *MLL* with those of a fusion partner, yielding a newly formed chimeric protein with an altered function that endows hematopoietic progenitors with self-renewing and leukemogenic activity (Eguchi M, 2005). Although the molecular basis for the oncogenic activity of MLL chimeric proteins is not completely understood, it seems to be derived, at least in part, through activation of clustered homeobox (HOX) genes (Harper & Aplan, 2008).

Translocations involving chromosome 11q23, where the *MLL* gene is located, are typical aberrations observed in adults with t-AML, where the frequency is significantly higher compared to de novo AML cases – 9.4% vs. 2.6% (Schoch et al., 2003). Frequent partners are chromosomes 9, 19 and 4 in the t(9;11), t(19;11) and t(4;11) translocations. Particularly higher frequency in t-AML was reported in regard to t(9;11), compared to de novo AML - 11% versus 1% respectively (Kayser et al., 2011). Besides, some structural differences between de novo AML and t-AML exist, although their clinical significance is still unclear. Typical examples of such differences are the t-AML with *MLL* rearrangements that, similarly to infant leukemias, have genomic breakpoints in *MLL* tending to cluster in the 3' portion, in contrast to adults with de novo AML, in whom the breakpoint is located in the 5' portion of the

8.3 kb breakpoint cluster region (BCR) (Zhang & Rowley,2006). Younger age, a mean period of latency of 2 years and monocytic subtypes are characteristic features of this type of leukaemia (Leone et al., 2001).

6.2.2. Translocations involving chromosome 21q22 / AML1 (CBFA2/RUNX1) gene

T-AML with balanced 21q22 aberrations has been associated with prior exposure to radiation, epipodophyllotoxins, and anthracyclines. Translocations involving chromosome 21q22 comprise multiple abnormalities, presented as t(8;21) (56%), t(3;21) (20%), and t(16;21) (5%) (Slovak et al., 2002), t(1;21)/*RUNX1-PRDM16* (Sakai et al., 2005) and other partner chromosomes (Slovak et al., 2002). The median latency for 21q22 patients is 39 months, compared to 26 months for 11q23 patients, 22 months for inv(16), 69 months for rare recurring aberrations, and 59 months for Unique (nonrecurring) balanced aberration (Slovak et al., 2002).

6.2.3. Translocations involving chromosome 11p15/ NUP98 gene

The *NUP98* gene has been reported to be fused with at least 15 partner genes in leukemias with 11p15 translocations, including *PRRX1* (*PMX1*), *HOXD13*, *RAP1GDS1*, *HOXC13*, *TOP1*, etc. (Kobzev et al., 2004). The resultant chimeric transcripts encode fusion proteins that juxtapose the N-terminal GLFG repeats of *NUP98* to the C-terminus of the partner gene. Of note, several of these translocations have been found in patients with t-AML, suggesting that genotoxic chemotherapan important role in generating chromosomal rearrangements involving *NUP98* (Lam & Aplan, 2001).In a survey of childhood t-AML/t-MDS, 11p15 translocations were found in 6% of the cases, including t(11;17)(p15;q21), t(11;12)(p15;q13), t(7;11)(p15;p15), inv(11)(p15q22), and add(11)(p15) and it has been suggested that *NUP98* may be a target gene for t-AML/MDS, and that t-AML/MDS with a fusion of *NUP98* and *HOX* or *DDX10* genes may be more frequent in children than in patients of other age groups (Nishiyama et al.,1999).

6.2.4. Translocations associated with "favorable" prognosis

A relatively distinct subgroup of t-AML comprises patients bearing "favorable" cytogenetic abnormalities, such as inv(16) and t(15;17) (Andersen MK et al. 2002), and more rarely – t(8;21) (Gustafson et al., 2009). These aberrations have been observed after alkylating agents and/or topoisomerase II inhibitors. High frequency of t(15;17), inv(16) and t(8;21) (18-29%, 21%, and 15% respectively) has also been reported in patients treated with radiotherapy only (Andersen et al., 2002; Yin et al., 2005).

The median latency period after the treatment is 22 months in patients with inv(16), 29 months in patients with t(15;17) and 37 months in patients with t(8;21). More than half of the cases in each group had additional cytogenetic abnormalities. Trisomy of chromosomes 8, 21, 22 and del(7q) are the most frequent additional abnormalities in the inv(16) subgroup, whereas trisomy 8, monosomy 5, and del(16q) are most frequent in the t(15;17) subgroup. Additional abnormalities commonly associated with t(8;21) include loss of a sex chromosome and Trisomy 4 (Andersen et al., 2002; Gustafson et al., 2009; Yin et al., 2005).

Interestingly, some structural differences were observed between patients positive for these aberrations with de novo AML and t-AML.In t-AML with inv(16)/t(16;16), the unusual rare types of fusion *CBFB-MYH11* transcripts were found to be significantly more frequent compared to de novo AML (Schnittger et al., 2007).

In therapy related t(15;17) APL, a prevalence of short form of *PML-RARa* transcripts (bcr3) was reported (62% of cases), while in de novo APL, the frequency of cases with a short form varied from 15% to 40-47% (Lin et al., 2004; Douer et al., 2003). On the other hand, in 39% of t-APL exposed to mitoxantrone (a topoisomerase II poison) and in none of the cases arising de novo, the translocation breakpoints are tightly clustered in an 8-bp region within *PML* intron 6, associated with the synthesis of long (bcr1) (Mistry et al., 2005; Hasan et al., 2010). In functional assays, this "hot spot" and the corresponding RARA breakpoints were common sites of mitoxantrone-induced cleavage by topoisomerase II (Mistry et al.,2005).

As to *RARA* breakpoints, significant clustering of *RARA* breakpoints in a 3' region of intron 2 (region B) was found in 65% of t-APL as compared to 28% de novo APLs. Furthermore, approximately 300 bp downstream of *RARA* region B contained a sequence highly homologous to a topoisomerase II consensus sequence. Biased distribution of DNA breakpoints at both *PML* and *RARA* loci suggests the existence of different pathogenetic mechanisms in t-APL as compared with de novo APL (Hasan et al., 2010). Furthermore, a significant breakpoint clustering has been also observed in *PML* and *RARA* loci, with *PML* breakpoints lying outside the mitoxantrone-associated hotspot region in epirubicin-related t-APL, that were shown to be preferential sites of topo II-induced DNA damage, enhanced by epirubicin (Mays et al., 2010).

On the other hand, almost all chromosome translocations in leukemia that have been analyzed to date show no consistent homologous sequences at the breakpoint with small deletions and duplications in each breakpoint, and micro-homologies and non-template insertions at genomic junctions of each chromosome translocation. The size of these deletions and duplications in the same translocation is much larger in de novo leukemia than in therapy-related leukemia (Zhang & Rowley, 2006).

6.3. Molecular abnormalities, unrelated to chromosome aberrations

Several molecular abnormalities were identified in both de novo AML and t-AML that are not a result of chromosome abnormalities, including mainly point mutations and gene tandem duplications. Significant differences in frequency of some of them were reported in t-AML.

Internal tandem duplications (ITD) and point mutations within the tyrosine kinase domain (TKD) of the FMS-like tyrosine kinase 3 (*FLT3*) gene are among the most frequent molecular abnormalities in de novo AML, accounting for more than 22% - 35% of the cases, and showing significant associations with the presence of a normal karyotype. In contrast, these mutations are only rarely seen in t-AML (Qian et al., 2010). Interestingly, in a small study of t-APL, *FLT3* mutations were detected in 42% of the patients, an incidence similar to that found in de novo APL cases (30%) (Chillón et al., 2010). These results and the preferential use of S-form of *PML-RARA* transcripts suggest that different molecular mechanisms are in-

volved in t-APL compared with de novo APL (Yin et al., 2005). *NPM1* and *CEBPA* mutations, that are generally associated with favorable prognosis, are also detected with a significantly lower frequency – 30% to 40-50% and 15-20%, respectively, in de novo AML compared to 4-5% and less in t-AML (Pedersen-Bjergaard et al., 2007; Kayser et al., 2011).

In contrast, higher incidence in t-AML was reported for *TP53* mutations – 20% to 30% versus 10-15% in de novo AML. The spectrum of mutations includes missense mutations in exons 4–8, as well as loss of the wild type allele, typically as a result of a cytogenetic abnormality of 17p. In t-MDS/t-AML, *TP53* mutations are associated with −5/del(5q) and a complex karyotype (Pedersen-Bjergaard et al., 2007; Qian et al., 2010).

Point mutations in the *RUNX1* gene are another mode of genetic alteration in development of leukemia, in addition to gene rearrangements associated with chromosomal translocation. Sporadic point mutations are frequently found in three leukemia entities: AML M0 subtype, MDS-AML, and secondary (therapy-related) MDS/AML. In t-MDS/t-AML, as well as after atomic bomb radiation exposure, the reported incidence for point mutations was higher (15–30%), frequently with an association with activating mutations of the RAS pathway, compared to de novo disease (2-3%). Mutations are commonly located in the N-terminal Runt homology domain (RHD) or in the C-terminal region including the transactivation domain (TAD) and could be found in patients treated in alkylating agents (Osato M., 2004). Cases with *RUNX1* mutations usually present as t-MDS, with deletion or loss of chromosome arm 7q and with subsequent transformation to overt t-AML (Christiansen et al., 2004). In contrast, in de novo AML, *RUNX1* mutations are most frequent in cases with +13, whereas frequencies are similar in other cytogenetic groups (26%-36%) (Schnittger et al.,2007). No significant differences have been reported in regard to *NRAS*, *KRAS*, *MLL-PTD*, *PTPN11*, *JAK2*.

To study the frequency and spectrum of molecular abnormalities with a proven or suggestive role in leukemic transformation in patients with t-AML we analysed 407 consecutive adult AML patients, diagnosed and treated in our institution, for a 12-years period. Among them, 26 cases had history for a previous malignancy treated with chemotherapy and/or radiotherapy which accounts for 6,1% of the cases – 12 (46%) males and 14 (54%) females, at a mean age of 53.5 years (ranging 22-83 years).AML was diagnosed after radio and/or chemotherapy for solid tumours in 16 (61.5%) of the patients and haematopoietic neoplasms – in 10 (38.5%). Qualitative, semi-quantitative or quantitative real-time Reverse transcription polymerase chain reaction (RT-PCR) was applied in all patients for screening of molecular abnormalities, as follows: (i) fusion transcripts *BCR-ABL* (P210; P190), *PML-RARA*, *AML1-ETO*, *CBFb-MYH11*, *MLL-AF9*, *MLL-AF6*, *DEK-CAN*, (ii) internal or partial tandem duplication of *FLT3* (*FLT3*-ITD) and *MLL* (*MLL*-ITD) genes respectively, (iii) aberrant over-expression of *Survivin*, *EVI1*, *BAALC*, *MLF1*, *PRAME*, *MDR1* and *AID* genes, and type A mutation of *NPM1* gene. At least one molecular marker was detected in all patients. The most frequent type of molecular abnormalities were the aberrant gene over-expression. Among the overexpressed genes, *MDR1* over-expression was the most common finding. The established frequency (61.5%) was significantly higher compared to that in patients with de novo AML (25.0%) (Schaich et al., 2004). Molecular equivalents of recurrent translocations according to the WHO classification (2008) were found in 34.6% of the cases [9/26]. The "favoura-

ble" fusion transcripts *PML-RARA*, *CBFb-MYH11*, *AML1-ETO* were detected in 30.8% of t-AML, and their frequency was similar to that reported in de novo AML (Grimwade et al., 2010). In contrast, the *MLL*-PTD was significantly more frequent (11.5%) compared to de novo AML (5.0%) (Patel et al., 2012), while the incidence of *FLT3*-ITD was significantly lower (7.7% vs 25-25%) (Kindler et al., 2010). Despite the remarkable heterogeneity of detected molecular abnormalities, three groups of t-AML could be defined including: patients with "favourable" fusion transcripts,patients with overexpression of multiple "unfavourable" genes, and patients without a specific pattern (Data presented on Table 5.).

Eight of the patients (30.8%) beared "favourable" fusion transcripts *PML-RARA*, *CBFb-MYH11*, or *AML1-ETO* mRNA. In addition, *PRAME*(+) was observed in 3/7 evaluable cases, as well as *FLT3*-ITD, *Survivin*(+) and *NPM1* mutation – found in 1 case each. *MDR1*overexpression was found in 5/8 (62.5%) patients. Interestingly, the patients in this group were significantly younger compared to the remaining patients (41.9 yrs vs 57.8 yrs, respectively). The analysis identified 7 (26.7%) patients with with multiple "unfavourable" abnormalities - *BAALC* and *Survivin* genes were overexpressed in 7/7 cases, in combination with *EVI1* gene overexpression in 5/7 patients or *MLF1* – in 4/7, *MLL*-PTD – in 2/7, *FLT3*-ITD - in 1/7. Interestingly ≥3 concomitant arerrations were detected in 6/7 cases. *MDR1* overexpression was found in all patients. The remaining 11 (42.3%) patients did not show any specific pattern. Single molecular abnormalities such as *MLL*-PTD; *MLL-AF9*; *EVI1* gene overexpression, associated with *Survivin*(+) in half of the cases were observed, while *MDR1* overexpression was found in 5/11 (45.4%) patients. Clinical observation revealed 6 cases of early deaths. The OS was significantly different in the three groups (log rank test p=0.006) being the worst in patients with with multiple "unfavourable" abnormalities and the best – in the "favourable"fusion transcripts group (Balatzenko & Guenova, 2012).

6.4. Cooperating mutations in MDS and AML

According to the model proposed by Deguchi & Gilliland (2002), development of AML is the consequence of collaboration between at least two broad classes of mutations: (i) class I mutations which result in constitutively activated tyrosine kinases (gain of function) and confer a proliferative and/or survival advantage without affecting differentiation - *c-KIT* D816, *FLT3*-ITD; *FLT3* D835Y; N- or K-*RAS* mutations; *PTPN11*; *JAK3*; and (ii) class II mutations that affect genes encoding hematopoietic transcription factors (loss of function) and serve primarily to impair hematopoietic differentiation - *RUNX1-EVI1*; *RUNX1-ETO*; *CBFb-MYH11*; *MLL* fusions; *NUP98-HOXA9*; *C/EBPa*; *PU.1*; *NPM1* (Deguchi & Gilliland, 2002; Stavropoulou et al., 2010). In a recent study of 140 cases of t-AML, 33 (26%) showed evidence of Class I mutations, 47 (34%) - of Class II mutations, and only 18 (13%) demonstrated both Class I and Class II mutations (Pedersen-Bjergaardet al., 2006). Several studies confirm the applicability of the model of collaboration between the classes of mutations in t-AML.

At least 14 different genes have been identified as mutated in t-MDS and t-AML, clustering differently and characteristically in the eight genetic pathways. Class I and Class II mutations are significantly associated, indicating their cooperation in leukemogenesis (Pedersen-Bjergaard et al., 2007). Several examples of such cooperative genetic alterations were reported.

Group	Patient's age and gender	*BCR-ABL*	*PML-RARA*	*AML-ETO*	*CBFb-MYH11*	*MLL-AF9*	*MLL-AF6*	*MLL-PTD*	*FLT3-ITD*	*DEK-CAN*	*EVI1*	*BAACL*	*MLF1*	*PRAME*	*MDR1*	*Survivin*	*AID*	*NPM1 Mut A*
I n=8 30.8%	52/m	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	62/f	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	49/f	0	1	0	0	0	0	0	1	0	0	0	0	1	1	0	0	0
	23/f	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	1
	27/f	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	72/m	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	28/m	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0
	22/m	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0
II n=7 26.9%	67/f	0	0	0	0	0	0	0	1	0	0	1	1	0	1	1	0	0
	48/f	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	0	1
	65/f	0	0	0	0	0	0	0	0	0	1	1	0	0	1	1	0	0
	50/f	0	0	0	0	0	0	1	0	0	1	1	1	1	1	1	0	0
	30/m	0	0	0	0	0	0	1	0	0	1	1	0	0	1	1	0	1
	57/m	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	0	0
	82/m	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0
III n=11 42.3%	57/f	0	0	0	0	0	0	0	0	0	1	0	1	0	1	N	0	0
	83/m	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	74/m	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	N
	44/f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	67/f	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1
	47/f	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
	56/m	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	55/f	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	68/m	0	0	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0
	49/m	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	41/f	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Total		0%	11.5%	11.5%	7.7%	3.8%	0%	11.5%	7.7%	0%	23.1%	26.9%	24.0%	15.4%	61.5%	48.0%	0%	16%

Table 5. Molecular alterations in therapy-related acute myeloid leukemias. Group I - patients with "favourable" fusion transcripts, Group II - patients with overexpression of multiple "unfavourable" genes, Group III - patients without a specific pattern. Abreviations: f – female, m – male, N – not done.

Mutations of *RUNX1* are common in therapy-related myelodysplasia following therapy with alkylating agents and are significantly associated with deletion or loss of chromosome arm 7q and with a subsequent leukemic transformation. *FLT3* mutation and trisomy 21 are thought to be second hits in AML with *RUNX1* Mutations (Osato M., 2004; Christiansen et al., 2004). Another example that supported cooperation between Class I and Class II mutations in leukemogenesis is the report of 4 cases with mutations of the *PTPN11* gene; 3 of which had -7/7q-, 2 cases had rare balanced translocations to chromosome band 21q22 with rearrangement of the *RUNX1* gene and the other two patients had rare balanced translocations to chromosome band 3q26 with a rearrangement of the *EVI1* gene (Christiansen et al., 2007). Significant association had also been reported between –5/5q– and *p53* mutations and complex chromosome rearrangements; *MLL* rearrangements and mutations of *NRAS*, *KRAS* or *BRAF*; *PML-RARA* and *FLT3*-ITD; *RUNX1* mutations (Class II) and *N-RAS* mutation (Class I); *MLL-CBP* (Class II) and *FLT3*-ITD (Class I), etc. (Imagawa et al., 2010). Many of the associations observed in t-AML, such as the *NPM1-FLT3*, *AML1-cKIT* and *RARA-FLT3* combinations, have previously been emphasized in de novo AML. According to Pedersen-Bjergaard et al., 2007, in t-AML, at least 8 alternative genetic pathways have been defined based on characteristic recurrent chromosome abnormalities: (i) patients with 7q–/–7 but normal chromosomes 5 and without balanced aberrations, (ii) patients with 5q–/–5, but without balanced aberrations; (iii) patients with t-AML and balanced translocations involving the chromosomal band 11q23, resulting in chimeric rearrangements between the MLL gene and one of its numerous alternative partner genes; (iv) patients with balanced translocations to chromosome band 21q22 or inv(16); (v) patients with promyelocytic leukemia and chimeric rearrangement of the PML and RARA genes; (vi) patients with chimeric rearrangement of the NUP98 gene on 11p15; (vii) patients with a normal karyotype; (viii) patients with other, often unique chromosome aberrations.

7. Prognostic factors

The diagnosis of therapy-related myeloid leukemia (t-MDS/t-AML) identifies a group of high-risk patients with multiple and varied poor prognostic features (Larson, 2007), such as overrepresentation of 11q23 translocations, adverse cytogenetics, including complex and monosomal karyotypes, and *MDR1* gene overexpression, as well as reduced frequency of "favorable" *NPM1*, and *CEBPA* mutations. Besides, frequent comorbidities and cummulative toxicities, related to previous cytotoxic treatments also contribute to a worse prognosis compared to de novo AML (D'Alò et al., 2011; Kayser S, et al., 2011). In a recent study, the outcome of patients with t-AML was significantly inferior in comparison to de novo AML: the 4-year relapse-free survival (RFS) was 24.5% versus 39.5%; and the 4-year overall survival (OS) was of 25.5% versus and 37.9%, respectively (Kayser et al., 2011). During the follow-up of 109 t-AML patients after treatment for epithelial ovarian carcinoma, a median survival of 3 months from the time of secondary leukemia diagnosis was found compared to 6 month in patients with de novo AML (Vay et al., 2011). Schoch et al., 2004 found significantly shorter median OS in t-AML than in de novo AML (10 vs 15 months). Within patients with t-

AML, there were significant correlations between OS and both unfavorable and favorable cytogenetics, while age and WBC count had no impact on OS (Schoch et al., 2004). The critical impact of karyotype on the prognosis was reported by Kern et al., clearly demonstrated significant differences in the median survival between t-AML patients groups with favorable karyotype (26.7 months) and unfavorable karyotype (5.6 months) (Kern et al., 2004).

Encouraging results were reported after allogeneic hematopoietic stem cells transplantation (allo-HSCT). The follow-up of 461 patients with t-MDS or t-AML who underwent allo-HSCT detected 3-year RFS and OS rates of 33% and 35%, respectively. In a multivariate analysis, the following risk factors were identified: (1) not being in complete remission at the time of transplantation, (2) abnormal cytogenetics, (3) higher patients' age and (4) therapy-related MDS. Using age (<40 years), abnormal cytogenetics and not being in complete remission at the time of transplantation as risk factors, three different risk groups with OS of 62%, 33% and 24% could be easily distinguished (Kröger et al., 2009). Similar results were observed by Litzow et al., 2010. The analysis of outcomes in a total of 868 patients, including t-AML (n=545) or t-MDS (n=323), revealed disease-free (DFS) and OS of 32% and 37% at 1 year and 21% and 22% at 5 years, respectively. In a multivariate analysis, 4 risk factors with adverse impacts on DFS and OS were identified: (1) age older than 35 years; (2) poor-risk cytogenetics; (3) t-AML not in remission or advanced t-MDS; and (4) donor other than an HLA-identical sibling or a partially or well-matched unrelated donor. The 5-years survival for subjects with none, 1, 2, 3, or 4 of these risk factors was 50%, 26%, 21%, 10%, and 4%, respectively [Litzow et al.,2010].

T-AMLs with "favorable" genetic abnormalities involving CBF-transcription complex - t(8;21)/*RUNX1-ETO* and inv(16)/t(16;16)/*CBFβ-MYH1* and APL with t(15;17)/*PML-RARα* are of particular interest since the reported results concerning the prognostic significance of these aberrations are contradictory and vary from study to study.

According to some studies these patients have treatment outcome comparable with primary AML patients (de Witte et al., 2002). Complete remission can be obtained in 85% of intensively treated patients with inv(16), and in 69% with t(15;17), with a median OS of 29 months in both cytogenetic subgroups, thus the response rates to intensive chemotherapy are comparable to those of de novo disease (Andersen et al., 2002). Similarly, t-AML with t(15;17) and t(8;21), treated according to standard protocols, had an outcome similar to de novo cases, indicating the dominant prognostic role of good karyotypes (D'Alò et al., 2011). The comparison of clinical and pathologic findings in therapy-related APL and de novo APL cases revealed abnormal promyelocytes with similar morphologic and immunophenotypic features, comparable cytogenetic findings, comparable rates of FMS-like tyrosine kinase mutations, and similar rates of recurrent disease and death, suggesting that secondary APL is similar to de novo APL and, thus, should be considered distinct from other secondary acute myeloid neoplasms (Duffield et al., 2012).

In contrast, matched analysis (by age, Eastern Cooperative Oncology Group performance status, and additional cytogenetic abnormalities) indicated worse OS and event-free survival (EFS) in patients with therapy-related CBF AML carrying the recurrent chromosomal aberrations inv(16) or t(8;21) – a median OS of 100 weeks compared to 376 weeks in de novo CBF AMLs (Borthakuret al., 2009). In patients with t-AML and t(8;21), the OS is significantly infe-

rior to that of patients with de novo t(8;21) AMLs (19 months vs not reached). These findings suggest that t(8;21) t-AMLs share many features with de novo AML with t(8;21)(q22;q22), but the affected patients have a worse outcome (Gustafson et al., 2009). Interstingly, it has been reported recently that despite that fewer complete remissions are achieved in t-APL (63.6%) compared to de novo APL (92.5%), this was a result of the higher induction mortality rate of 36.4% vs. 7.5%, respectively. No cases of leukemic resistance were seen in either group. However, OS was also inferior in t-APL compared to de novo APL (51% vs. 84%, respectively) (Elliott et al., 2012).

8. Treatment

The survival of patients with t-AML is often poor despite prompt diagnosis and treatment. There is a paucity of prospective treatment data since these patients are often excluded from frontline chemotherapy trials and turned to best supportive care. However, despite that the CR rate of t-AML patients (28% up to 50%) has been demonstrated to be inferior to patients with de novo AML (65-80%), this difference can be attributed to the higher number of patients with unfavourable karyotypes. Within cytogenetically defined subgroups, the prognosis of t-AML patients does not differ significantly from patients with de novo AML. Treatment recommendations should be further based on the patient's performance status, which likely reflects age, comorbidities, the status of the primary disease, and the presence of complications from primary therapy, as well as the clonal abnormalities detected in the t-AML cells. Standard chemotherapy, haematopoietic stem cell transplantation, as well as experimental trials are applied.

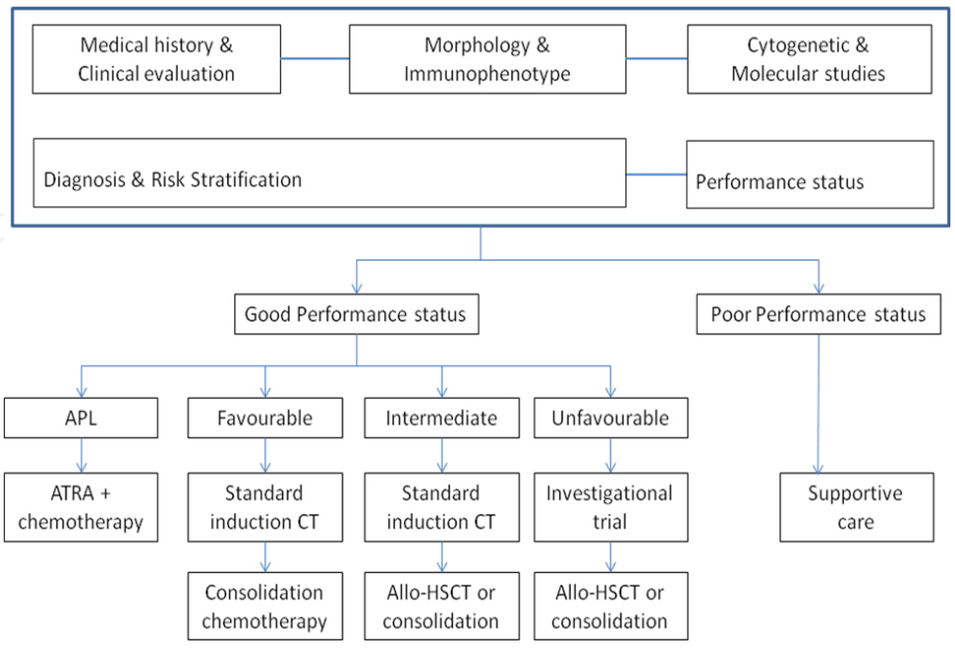

Figure 1. Clinical algorythm in the management of t-AML patients.

Intriguingly, several studies found that results after induction therapy were not different between t-AML and de novo AML patients. Furthermore, analyses of CR-rates, OS and DFS, when corrected for the influence of age, cytogenetic abnormalities, performance status and leucocyte count, showed that the presence of a t-AML may even lose prognostic significance and patients with secondary AML should be offered the chance of benefiting from treatment according to current frontline AML protocols (Ostgård et al., 2010). The dosage and modality of treatment during postremission therapy however have a marked impact on the cumulative toxicity of cancer therapy. Therefore, intensive induction therapy should not be withheld for t-AML patients, and dose-reduced regimes for allogeneic HSCT should be considered. In contrast, t-AML patients >60 years show a significantly greater relapse rates probably due to the lower dosage of applied chemotherapy during postremission therapy compared with younger patients (Kayser et al., 2011). Encouraging results are reported after allogeneic transplantation. The identification of relevant risk factors allows for a more precise prediction of outcome and identification of subjects most likely to benefit from allogeneic transplantation.Allogeneic transplantation should be proposed timely to these patients after an accurate analysis of patient history (Litzow et al., 2010; Spina et al., 2012). Novel transplantation strategies using reduced intensity conditioning regimens as well as novel drugs – demethylating agents and targeted therapies, await clinical testing and may improve outcome (de Witte et al., 2002).

9. Conclusion

As the number of patients with t-AMLs is expected to rise, safety issues of cytotoxic therapies are becoming increasingly important in order to develop strategies to reduce the risk for therapy-related malignancies without compromising success rates for the respective primary disorders. Besides, there is clinical and biological overlap between therapy related and high-risk de novo leukaemias suggesting similar mechanisms of leukaemogenesis. Deeper insights into pathogenetic mechanisms will eventually help to establish a more differentiated clinical approach to successfully treat, but hopefully also prevent, these often fatal consequences of cytotoxic therapies.

Acknowledgements

The reported own data on therapy-related AML were generated in the Center of Excellence "Translational Research in Haematology" of the National Specialised Hospital for Active Treatment of Hematological Diseases, supported by National Science Fund (grant CVP01-119/D02-35/2009), as follows: morphology and immunophenotype were evaluated at the Laboratory of Haematopathology and Immunology, cytogenetic and molecular studies were performed at the Laboratory of Cytogenetics and Molecular Biology, clinical management was performed at the Haematology Clinic. MG and GB contributed equally to the development of the manuscript. GM was responsible for the treatment section. MG and GB

have been supported by EuGESMA COST Action BM0801: European Genetic and Epigenetic Study on AML and MDS.

Author details

Margarita Guenova[1,4*], Gueorgui Balatzenko[2,4] and Georgi Mihaylov[3,4]

*Address all correspondence to: margenova@gmail.com

1 Laboratory of Haematopathology and Immunology, National Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria

2 Laboratory of Cytogenetics and Molecular Biology, National Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria

3 Haematology Clinic, National Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria

4 Center of Excellence – Translational Research in Haematology, National Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria

References

[1] Abbas, S., Lugthart, S., Kavelaars, F. G., Schelen, A., Koenders, J. E., Zeilemaker, A., van Putten, W. J., Rijneveld, A. W., Löwenberg, B., & Valk, P. J. Acquired mutations in the genes encoding IDH1 and IDH2 both are recurrent aberrations in acute myeloid leukemia: prevalence and prognostic value. Blood. (2010). , 116(12), 2122-6.

[2] Ahmad F, Mandava S, Das BR. Mutations of NPM1 gene in de novo acute myeloid leukaemia: determination of incidence, distribution pattern and identification of two novel mutations in Indian population. Hematol Oncol. 2009;27(2):90-7.

[3] Allan, J. M., Wild, Rollinson. S., Willett, E. V., Moorman, A. V., Dovey, G. J., Roddam, P. L., Roman, E., Cartwright, R. A., & Morgan, G. J. Polymorphism in glutathione S-transferase is associated with susceptibility to chemotherapy-induced leukemia. Proc Natl Acad Sci U S A. (2001). , 1.

[4] Andersen, M. K., Johansson, B., Larsen, S. O., & Pedersen-Bjergaard, J. Chromosomal abnormalities in secondary MDS and AML.Relationship to drugs and radiation with specific emphasis on the balanced rearrangements.Haematologica. (1998). Jun;, 83(6), 483-8.

[5] Andersen, M. K., Christiansen, D. H., Kirchhoff, M., & Pedersen-Bjergaard, J. Duplication or amplification of chromosome band 11q23, including the unrearranged MLL

gene, is a recurrent abnormality in therapy-related MDS an dAML, and is closely related to mutation of the TP53 gene and to previous therapy with alkylating agents. Genes Chromosomes Cancer. (2001). , 31(1), 33-41.

[6] Andersen, M. K., Larson, R. A., Mauritzson, N., Schnittger, S., Jhanwar, S. C., & Pedersen-Bjergaard, J. Balanced chromosome abnormalities inv(16) and t(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: report from an international workshop. Genes Chromosomes Cancer. (2002). , 33(4), 395-400.

[7] Andersen, M. K., Christiansen, D. H., & Pedersen-Bjergaard, J. Centromeric breakage and highly rearranged chromosome derivatives associated with mutations of TP53 are common in therapy-related MDS and AML after therapy with alkylating agents: an M-FISH study. Genes Chromosomes Cancer. (2005). , 42(4), 358-71.

[8] Anderson, L. A., Pfeiffer, R. M., Landgren, O., Gadalla, S., Berndt, S. I., & Engels, E. A. Risks of myeloid malignancies in patients with autoimmune conditions. Br J Cancer. (2009). , 100(5), 822-8.

[9] Arber, D. A., Slovak, M. L., Popplewell, L., Bedell, V., Ikle, D., Rowley, , International, Workshop., on, Leukemia., Karyotype, , & Prior, Therapy. Therapy-related acute myeloid leukemia/myelodysplasia with balanced 21q22 translocations.Am J Clin Pathol. (2002). , 117(2), 306-13.

[10] Askling, J., Fored, C. M., Baecklund, E., Brandt, L., Backlin, C., Ekbom, A., et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. (2005). , 64(10), 1414-20.

[11] Au, W. Y., Wan, S. K., Man, T. S., Kwong, C., & , Y. L. Pentasomy 8q in therapy-related myelodysplastic syndrome due to cyclophosphamide therapy for fibrosing alveolitis. Cancer Genet Cytogenet. (2003). , 141(1), 79-82.

[12] Bacher, U., Haferlach, C., Schnittger, D., Alpermann, T., Kern, W., & Haferlach, T. Patients with Therapy-Related Myeloid Disorders Share Genetic Features but Can Be Separated by Blast Counts and Cytogenetic Risk Groups Into Prognostically Relevant Subgroups, Blood (ASH Annual Meeting Abstracts), (2011). Abstract 3583

[13] Bacher U, Haferlach T, Kern W, Haferlach C, Schnittger S.A comparative study of molecular mutations in 381 patients with myelodysplastic syndrome and in 4130 patients with acute myeloid leukemia.Haematologica. 2007;92(6):744-52.

[14] Balatzenko, G., & Guenova, M. Spectrum of molecular alterations in therapy-related acute myeloid leukemias. COST Action:BM0801: 8th MC meeting & 6th WG meeting. April (2012). Beldrade, Serbia, 23-24.

[15] Barlogie, B., Tricot, G., Haessler, J., van Rhee, F., Cottler-Fox, M., Anaissie, E., Waldron, J., Pineda-Roman, M., Thertulien, R., Zangari, M., Hollmig, K., Mohiuddin, A., Alsayed, Y., Hoering, A., Crowley, J., & Sawyer, J. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to

poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood. (2008). , 111(1), 94-100.

[16] Barnard DR, Woods WG.Treatment-related myelodysplastic syndrome/acute myeloid leukemia in survivors of childhood cancer--an update. Leuk Lymphoma. (2005). , 46(5), 651-63.

[17] Beekman R, Touw IP. G-CSF and its receptor in myeloid malignancy.Blood. 2010;115(25):5131-6.

[18] Bennett, J. M., Troxel, A. B., Gelman, R., Falkson, G., Coccia-Portugal, Dreicer. R., Tormey, D. C., & Rushing, D. Myelodysplastic syndrome and acute myeloid leukemia secondary to mitolactol treatment in patients with breast cancer. J Clin Oncol. (1994). , 12(4), 874-5.

[19] Bhatia, S., Robison, L. L., Oberlin, O., Greenberg, M., Bunin, G., Fossati-Bellani, F., & Meadows, A. T. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med. (1996). , 334(12), 745-51.

[20] Bhavnani M, Azzawi SA, Yin JA, Lucas GS.Therapy-related acute promyelocytic leukaemia.Br J Haematol. 1994;86(1):231-2.

[21] Blanco, J. G., Dervieux, T., Edick, Mehta. P. K., Rubnitz, J. E., Shurtleff, S., Raimondi, S. C., Behm, F. G., Pui, C. H., & Relling, M. V. Molecular emergence of acute myeloid leukemia during treatment for acute lymphoblastic leukemia. Proc Natl Acad Sci U S A. (2001). , 98(18), 10338-43.

[22] Bo, J., Schrøder, H., Kristinsson, J., Madsen, B., Szumlanski, C., Weinshilboum, R., Andersen, J. B., & Schmiegelow, K. Possible carcinogenic effect of 6-mercaptopurine on bone marrow stem cells: relation to thiopurine metabolism. Cancer.(1999). , 86(6), 1080-6.

[23] Bodner SM, Naeve CW, Rakestraw KM, Jones BG, Valentine VA, Valentine MB, Luthardt FW, Willman CL, Raimondi SC, Downing JR, Roussel MF, Sherr CJ, Look AT.Cloning and chromosomal localization of the gene encoding human cyclin Dbinding Myb-like protein (hDMP1). Gene. (1999).,229(1-2), 223-8.

[24] Bogni, A., Cheng, C., Liu, W., Yang, W., Pfeffer, J., Mukatira, S., French, D., Downing, J. R., Pui, C. H., & Relling, M. V. Genome-wide approach to identify risk factors for therapy-related myeloid leukemia.Leukemia. (2006). , 20(2), 239-46.

[25] Boice Jr, Greene. M. H., Killen, J. Y., Jr Ellenberg, S. S., Keehn, R. J., Mc Fadden, E., Chen, T. T., Fraumeni, J. F., & Jr , . Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). N Engl J Med. (1983). , 309(18), 1079-84.

[26] Bolufer, P., Collado, M., Barragan, E., Calasanz, Colomer. D., Tormo, M., González, M., Brunet, S., Batlle, M., Cervera, J., & Sanz, . Profile of polymorphisms of drug-metabolising enzymes and the risk of therapy-related leukaemia.Br J Haematol. (2007). , 136(4), 590-6.

[27] Borthakur, G., Lin, E., Jain, N., Estey, Cortes. J. E., O'Brien, S., Faderl, S., Ravandi, F., Pierce, S., & Kantarjian, H. Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. Cancer. (2009). , 115(14), 3217-21.

[28] Boultwood, J., Fidler, C., Strickson, A. J., Watkins, F., Gama, S., Kearney, L., Tosi, S., Kasprzyk, A., Cheng, J. F., Jaju, R. J., & Wainscoat, J. S. Narrowing and genomic annotation of the commonly deleted region of the 5q- syndrome.Blood. (2002). , 99(12), 4638-41.

[29] Carli, P. M., Sgro, C., Parchin-Geneste, N., Isambert, N., Mugneret, F., Girodon, F., & Maynadié, M. Increase therapy-related leukemia secondary to breast cancer. Leukemia. (2000). , 14(6), 1014-7.

[30] Chak LY, Sikic BI, Tucker MA, Horns RC Jr, Cox RS.Increased incidence of acute nonlymphocytic leukemia following therapy in patients with small cell carcinoma of the lung.J Clin Oncol. (1984). , 2(5), 385-90.

[31] Chakraborty, S., Sun, C. L., Francisco, L., Sabado, M., Li, L., Chang, K. L., Forman, S., Bhatia, S., & Bhatia, R. Accelerated telomere shortening precedes development of therapy-related myelodysplasia or acute myelogenous leukemia after autologous transplantation for lymphoma. J Clin Oncol. (2009). , 27(5), 791-8.

[32] Chandra, P., Luthra, R., Zuo, Z., Yao, H., Ravandi, F., Reddy, N., Garcia-Manero, G., Kantarjian, H., & Jones, D. Acute myeloid leukemia with t(9;11)(q23): common properties of dysregulated ras pathway signaling and genomic progression characterize de novo and therapy-related cases. Am J Clin Pathol. (2010)., 133(5), 21-22.

[33] Chillón, M. C., Santamaría, C., García-Sanz, R., Balanzategui, A., Sarasquete, Alcoceba. M., Marín, L., Caballero, Vidriales. M. B., Ramos, F., Bernal, T., Díaz-Mediavilla, J., García de, Coca. A., Peñarrubia, Queizán. J. A., Giraldo, P., San, Miguel. J. F., & González, M. Long FLT3 internal tandem duplications and reduced PML-RARα expression at diagnosis characterize a high-risk subgroup of acute promyelocytic leukemia patients. Haematologica. (2010). , 95(5), 745-51.

[34] Christiansen, D. H., Andersen, M. K., Desta, F., & Pedersen-Bjergaard, J. Mutations of genes in the receptor tyrosine kinase (RTK)/RAS-BRAF signal transduction pathway in therapy-related myelodysplasia and acute myeloid leukemia. Leukemia. (2005). , 19(12), 2232-40.

[35] Christiansen DH, Andersen MK, Desta F, Pedersen-Bjergaard J. Mutations of genes in the receptor tyrosine kinase (RTK)/RAS-BRAF signal transduction pathway in therapy-related myelodysplasia and acute myeloid leukemia. Leukemia. 2005;19(12): 2232-40.

[36] Christiansen, D. H., Desta, F., Andersen, M. K., & Pedersen-Bjergaard, J. Mutations of the PTPN11 gene in therapy-related MDS and AML with rare balanced chromosome translocations. Genes Chromosomes Cancer. (2007). , 46(6), 517-21.

[37] Cimino, G., Papa, G., Tura, S., Mazza, P., Rossi, Ferrini. P. L., Bosi, A., Amadori, S., Lo, Coco. F., D'Arcangelo, E., Giannarelli, D., et al. Second primary cancer following Hodgkin's disease: updated results of an Italian multicentric study. J Clin Oncol. (1991). , 9(3), 432-7.

[38] Collins, C. M., Morgan, Mosse. C., & Sosman, J. Dacarbazine induced acute myeloid leukemia in melanoma. Melanoma Res. (2009). , 19(5), 337-40.

[39] Colovic, N., Suvajdzic, N., Kraguljac, Kurtovic. N., Djordjevic, V., Dencic, Fekete. M., Drulovic, J., Vidovic, A., & Tomin, D. Therapy-related acute leukemia in two patients with multiple sclerosis treated with Mitoxantrone. Biomed Pharmacother. (2012). , 66(3), 173-4.

[40] Cowell IG, Sondka Z, Smith K, Lee KC, Manville CM, Sidorczuk-Lesthuruge M, Rance HA, Padget K, Jackson GH, Adachi N, Austin CA. Model for MLL translocations in therapy-related leukemia involving topoisomerase IIβ-mediated DNA strand breaks and gene proximity. Proc Natl Acad Sci U S A. 2012;109(23):8989-94.

[41] Curtis, R. E., Boice, Stovall. M., et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med (1992). , 326, 1754-1.

[42] Czader M, Orazi A. Therapy-related myeloid neoplasms. Am J Clin Pathol. 2009;132(3):410-25.

[43] D'Alò, F., Fianchi, L., Fabiani, E., Criscuolo, M., Greco, M., Guidi, F., Pagano, L., Leone, G., & Voso, M. T. Similarities and differences between therapy-related and elderly acute myeloid leukemia.Mediterr J Hematol Infect Dis. (2011). e2011052

[44] Dann EJ, Rowe JM.Biology and therapy of secondary leukaemias. Best Pract Res Clin Haematol. (2001). , 14(1), 119-37.

[45] Dastugue N, Pris J, Colombies P. Translocation t(3;21)(q26;q22) in acute myeloblastic leukemia secondary to polycythemia vera. Cancer Genet Cytogenet.1990;44(2):275-6.

[46] de Witte, T., Oosterveld, M., Span, B., Muus, P., & Schattenberg, A. Stem cell transplantation for leukemias following myelodysplastic syndromes or secondary to cytotoxic therapy. Rev Clin Exp Hematol. (2002). , 6(1), 72-85.

[47] Deguchi, K., & Gilliland, D. G. Cooperativity between mutations in tyrosine kinases and in hematopoietic transcription factors in AML. Leukemia. (2002). , 16(4), 740-4.

[48] Devereux, S., Selassie, T. G., Vaughan, Hudson. G., Vaughan, Hudson. B., & Linch, D. C. Leukaemia complicating treatment for Hodgkin's disease: the experience of the British National Lymphoma Investigation. BMJ. (1990). , 301(6760), 1077-80.

[49] Diamandidou, E., Buzdar, A. U., Smith, T. L., Frye, D., Witjaksono, M., & Hortobagyi, G. N. Treatment-related leukemia in breast cancer patients treated with fluorouracil-doxorubicin-cyclophosphamide combination adjuvant chemotherapy: theUniversity of Texas M.D. Anderson Cancer Center experience. J Clin Oncol. (1996). , 14(10), 2722-30.

[50] Dissing, M., Le Beau-Bjergaard, Pedersen., & , J. Inversion of chromosome 16 and uncommon rearrangements of the CBFB and MYH11 genes in therapy-related acute myeloid leukemia: rare events related to DNA-topoisomerase II inhibitors? J Clin Oncol. (1998). , 16(5), 1890-6.

[51] Döhner, K., Brown, J., Hehmann, U., Hetzel, C., Stewart, J., Lowther, G., Scholl, C., Fröhling, S., Cuneo, A., Tsui, L. C., Lichter, P., Scherer, S. W., & Döhner, H. Molecular cytogenetic characterization of a critical region in bands 7q35-q36 commonly deleted in malignant myeloid disorders. Blood. (1998). , 92(11), 4031-5.

[52] Dores, G. M., Metayer, C., Curtis, R. E., Lynch, C. F., Clarke, E. A., Glimelius, B., Storm, H., Pukkala, E., van Leeuwen, F. E., Holowaty, E. J., Andersson, M., Wiklund, T., Joensuu, T., van't, Veer. M. B., Stovall, M., Gospodarowicz, M., & Travis, L. B. Second malignant neoplasms amonglong-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol. (2002). , 20(16), 3484-94.

[53] Douer, D., Santillana, S., Ramezani, L., Samanez, C., Slovak, M. L., Lee, Watkins. K., Williams, T., & Vallejos, C. Acute promyelocytic leukaemia in patients originating in Latin America is associated with an increased frequency of the bcr1 subtype of the PML/RARalpha fusion gene. Br J Haematol. (2003). , 122(4), 563-70.

[54] Drabløs, F., Feyzi, E., Vaagbø, P. A., Kavli, C. B., Bratlie, B., Peña-Diaz, J., Otterlei, M., Slupphaug, G., & Krokan, H. E. Alkylation damage in DNA and RNA--repair mechanisms and medical significance. DNA Repair (Amst). (2004). , 3(11), 1389-407.

[55] Duffield, Aoki. J., Levis, M., Cowan, K., Gocke, C. D., Burns, K. H., Borowitz-Ross, Vuica., & , M. Clinical and pathologic features of secondary acute promyelocytic leukemia. Am J Clin Pathol. (2012). , 137(3), 395-402.

[56] Eguchi, M., Eguchi-Ishimae, M., & Greaves, M. Molecular pathogenesis of MLL-associated leukemias. Int J Hematol. (2005). , 82(1), 9-20.

[57] Elliott, Letendre. L., Tefferi, A., Hogan, W. J., Hook, C., Kaufmann, S. H., Pruthi, R. K., Pardanani, A., Begna, K. H., Ashrani, Wolanskyj. A. P., Al-Kali, A., & Litzow, M. R. Therapy-related acute promyelocytic leukemia: observations relating to APL pathogenesis and therapy. Eur J Haematol. (2012). , 88(3), 237-43.

[58] Ellis NA, Huo D, Yildiz O, Worrillow LJ, Banerjee M, Le Beau MM, Larson RA,Allan JM, Onel K. MDM2 SNP309 and TP53 Arg72Pro interact to alter therapy-related acute myeloid leukemia susceptibility. Blood. 2008;112(3):741-9.

[59] Emerling BM, Bonifas J, Kratz CP, Donovan S, Taylor BR, Green ED, Le Beau MM, Shannon KM. MLL5, a homolog of Drosophila trithorax located within a segment of chromosome band 7q22 implicated in myeloid leukemia. Oncogene. 2002;21(31): 4849-54.

[60] Ezoe, S. Secondary Leukemia Associated with the Anti-Cancer Agent, Etoposide, a Topoisomerase II Inhibitor. Int J Environ Res Public Health. (2012). , 9(7), 2444-53.

[61] Faurschou, M., Sorensen, I. J., Mellemkjaer, L., Loft, A. G., Thomsen, Tvede. N., & Baslund, B. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol. (2008). , 35(1), 100-5.

[62] Felix CA.Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta. (1998).

[63] Felix CA, Hosler MR, Provisor D, Salhany K, Sexsmith EA, Slater DJ, Cheung NK,Winick NJ, Strauss EA, Heyn R, Lange BJ, Malkin D. The p53 gene in pediatric therapy-related leukemia and myelodysplasia.Blood. 1996;87(10):4376-81.

[64] Fisher, B., Rockette, H., Fisher, E. R., et al. Leukemia in breast cancer patients following adjuvant chemotherapy, or postoperative radiation: the NSABP experience. J Clin Oncol (1985). , 3, 1640-58.

[65] Flaig, T. W., Tangen, C. M., Hussain, M. H., Stadler, W. M., Raghavan, D., Crawford, E. D., Glodé, L. M., Southwest, Oncology., & Group, . Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial. J Clin Oncol. (2008). , 26(9), 1532-6.

[66] Fried I, Bodner C, Pichler MM, Lind K, Beham-Schmid C, Quehenberger F, Sperr WR, Linkesch W, Sill H, Wölfler A. Frequency, onset and clinical impact of somatic DNMT3A mutations in therapy-related and secondary acute myeloid leukemia. Haematologica. 2012;97(2):246-50.

[67] Gaidzik VI, Bullinger L, Schlenk RF, Zimmermann AS, Röck J, Paschka P, Corbacioglu A, Krauter J, Schlegelberger B, Ganser A, Späth D, Kündgen A,Schmidt-Wolf IG, Götze K, Nachbaur D, Pfreundschuh M, Horst HA, Döhner H, Döhner K. RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group. J Clin Oncol. 2011;29(10):1364-72

[68] Godley LA, Larson RA.Therapy-related myeloid leukemia.Semin Oncol. (2008). , 35(4), 418-29.

[69] Godley LA, Le Beau MM. Therapy-Related AML. In: Acute Myelogenous Leukemia, Ed. Karp JE, Humana Press Inc.,. (2007). 71-96.

[70] Greco, M., D'Alò, F., Scardocci, A., Criscuolo, M., Fabiani, E., Guidi, F., Di Ruscio, A., Migliara, G., Pagano, L., Fianchi, L., Chiusolo, P., Hohaus, S., Leone, G., & Voso, M. T. Promoter methylation of DAPK1, E-cadherin and thrombospondin-1 in de novo and therapy-related myeloid neoplasms.Blood Cells Mol Dis. (2010). , 45(3), 181-5.

[71] Green CL, Koo KK, Hills RK, Burnett AK, Linch DC, Gale RE.Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. J Clin Oncol. (2010). , 28(16), 2739-47.

[72] Griesinger, F., Metz, M., Trümper, L., Schulz, T., & Haase, D. Secondary leukaemia after cure for locally advanced NSCLC: alkylating type secondary leukaemia after in-

duction therapy with docetaxel and carboplatin for NSCLC IIIB. Lung Cancer. (2004). , 44(2), 261-5.

[73] Grimwade, D., Hills, R. K., Moorman, A. V., Walker, H., Chatters, S., Goldstone, A. H., Wheatley, K., Harrison, C. J., Burnett, A. K., National, Cancer., Research, Institute., Adult, Leukaemia., & Working, Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. Blood. (2010). , 116(3), 354-65.

[74] Guidelines for CarcinogenRisk Assessment.EPA/630/F. Risk Assessment Forum U.S. Environmental Protection Agency, Washington, DC, (2005). , 03.

[75] Guillem VM, Collado M, Terol MJ, Calasanz MJ, Esteve J, Gonzalez M, Sanzo C,Nomdedeu J, Bolufer P, Lluch A, Tormo M. Role of MTHFR (677, 1298) haplotype in the risk of developing secondary leukemia after treatment of breast cancer and hematological malignancies. Leukemia. 2007;21(7):1413-22.

[76] Gustafson, S. A., Lin, P., Chen, S. S., Chen, L., Abruzzo, L. V., Luthra, R., Medeiros, L. J., & Wang, S. A. Therapy-related acute myeloid leukemia with t(8;21) (q22;q22) shares many features with de novo acute myeloid leukemia with t(8;21)(q22;q22) but does not have a favorable outcome. Am J Clin Pathol. (2009). , 131(5), 647-55.

[77] Harada, Y., & Harada, H. Molecular mechanisms that produce secondary MDS/AML by RUNX1/AML1 point mutations. J Cell Biochem.(2011). , 112(2), 425-32.

[78] Harper DP, Aplan PD.Chromosomal rearrangements leading to MLL gene fusions: clinical and biological aspects. Cancer Res. (2008). , 68(24), 10024-7.

[79] Hasan SK, Ottone T, Schlenk RF, Xiao Y, Wiemels JL, Mitra ME, Bernasconi P, Di Raimondo F, Stanghellini MT, Marco P, Mays AN, Döhner H, Sanz MA, Amadori S,Grimwade D, Lo-Coco F. Analysis of t(15;17) chromosomal breakpoint sequences in therapy-related versus de novo acute promyelocytic leukemia: association of DNA breaks with specific DNA motifs at PML and RARA loci. Genes Chromosomes Cancer.2010;49(8):726-32.

[80] Haupt, R., Fears, T. R., Rosso, P., Colella, R., Loiacono, G., de Terlizzi, M., Mancini, A., Comelli, A., Indolfi, P., Donfrancesco, A., et al. Increased risk of secondary leukemia after single-agent treatment with etoposide for Langerhans' cell histiocytosis. Pediatr Hematol Oncol. (1994). , 11(5), 499-507.

[81] Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA.DNA repair pathways as targets for cancer therapy.Nat Rev Cancer. 2008;8(3):193-204.

[82] Hershman, D., Neugut, A. I., Jacobson, J. S., Wang, J., Tsai, W. Y., Mc Bride, R., Bennett, C. L., & Grann, V. R. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst. (2007). , 99(3), 196-205.

[83] Heuser M, Yap DB, Leung M, de Algara TR, Tafech A, McKinney S, Dixon J,Thresher R, Colledge B, Carlton M, Humphries RK, Aparicio SA. Loss of MLL5 results in pleiotropic hematopoietic defects, reduced neutrophil immune function, and extreme sensitivity to DNA demethylation. Blood. 2009;113(7):1432-43.

[84] Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, Razzouk BI, Ribeiro RC, Rubnitz JE, Sandlund JT, Rivera GK, Evans WE, Relling MV, Pui CH.Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA. 2007;297(11):1207-15.

[85] Howe, R., Micallef, I. N., Inwards, D. J., Ansell, S. M., Dewald, G. W., Dispenzieri, A., Gastineau, D. A., Gertz, Geyer. S. M., Hanson, Lacy. M. Q., Tefferi, A., & Litzow, M. R. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. Bone Marrow Transplant. (2003). , 32(3), 317-24.

[86] Imagawa, J., Harada, Y., Shimomura, T., Tanaka, H., Okikawa, Y., Hyodo, H., Kimura, A., & Harada, H. Clinical and genetic features of therapy-related myeloid neoplasms after chemotherapy for acute promyelocytic leukemia. Blood. (2010). , 116(26), 6018-22.

[87] Itzhar, N., Dessen, P., Toujani, S., Auger, N., Preudhomme, C., Richon, C., Lazar, V., Saada, V., Bennaceur, A., Bourhis, J. H., de Botton, S., & Bernheim, A. Chromosomal minimal critical regions in therapy-related leukemia appear different from those of de novo leukemia by high-resolution aCGH. PLoS One. (2011). e16623.

[88] Jawad, M., Seedhouse, C. H., Russell, N., & Plumb, M. Polymorphisms in human homeobox HLX1 and DNA repair RAD51 genes increase the risk of therapy-related acute myeloid leukemia. Blood. (2006). , 108(12), 3916-8.

[89] Jerez A, Yuka Sugimoto, Hideki Makishima, Amit Verma, Christine L O'Keefe, Ramon V Tiu, Azim M Mohamedali, Michael A McDevitt, Ghulam J. Mufti, Jacqueline Boultwood, and Jaroslaw P Maciejewski, Clinical and Genomic Characterization of Chromosome 7 Lesions in Myeloid Malignancies, Blood (ASH Annual Meeting Abstracts), 2011; 118: 3549.

[90] Joannides, M., & Grimwade, D. Molecular biology of therapy-related leukaemias. Clin Transl Oncol. (2010). , 12(1), 8-14.

[91] Johnson KJ, Blair CM, Fink JM, Cerhan JR, Roesler MA, Hirsch BA, Nguyen PL, Ross JA.Medical conditions and risk of adult myeloid leukemia.Cancer Causes Control. (2012). , 23(7), 1083-9.

[92] Josting, A., Wiedenmann, S., Franklin, J., May, M., Sieber, M., Wolf, J., Engert, A., Diehl, V., German, Hodgkin's., Lymphoma, Study., & Group, . Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. J Clin Oncol. (2003). , 21(18), 3440-6.

[93] Libura, J., Slater, D. J., & Felix, Richardson. C. Therapy-related acute myeloid leukemia-like MLL rearrangements are induced by etoposide in primary human CD34+ cells and remain stable after clonal expansion. Blood. (2005). Mar 1;, 105(5), 2124-31.

[94] Kaldor, J. M., Day, N. E., Clarke, E. A., Van Leeuwen, F. E., Henry-Amar, M., Fiorentino, M. V., Bell, J., Pedersen, D., Band, P., Assouline, D., et al. Leukemia following Hodgkin's disease. N Engl J Med. (1990). , 322(1), 7-13.

[95] Kaldor, J. M., Day, N. E., Pettersson, F., Clarke, E. A., Pedersen, D., Mehnert, W., Bell, J., Høst, H., Prior, P., Karjalainen, S., et al. Leukemia following chemotherapy for ovarian cancer. N Engl J Med. (1990). , 322(1), 1-6.

[96] Kayser S, Döhner K, Krauter J, Köhne CH, Horst HA, Held G, von Lilienfeld-Toal M, Wilhelm S, Kündgen A, Götze K, Rummel M, Nachbaur D, Schlegelberger B, Göhring G, Späth D, Morlok C, Zucknick M, Ganser A, Döhner H, Schlenk RF; German-Austrian AMLSG. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117(7): 2137-45.

[97] Kern, W., Haferlach, T., Schnittger, S., Hiddemann, W., & Schoch, C. Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. J Clin Oncol. (2004). , 22(12), 2510-1.

[98] Kindler T, Lipka DB, Fischer T. FLT3 as a therapeutic target in AML: still challenging after all these years. Blood. 2010;116(24):5089-102.

[99] Klymenko S, Trott K, Atkinson M, Bink K, Bebeshko V, Bazyka D, Dmytrenko I, Abramenko I, Bilous N, Misurin A, Zitzelsberger H, Rosemann M. Aml1 gene rearrangements and mutations in radiation-associated acute myeloid leukemia and myelodysplastic syndromes. J Radiat Res. 2005;46(2):249-55.

[100] Knight, J. A., Skol, A. D., Shinde, A., Hastings, D., Walgren, R. A., Shao, J., Tennant, T. R., Banerjee, M., Allan, J. M., Le Beau, Larson. R. A., Graubert, T. A., Cox, N. J., & Onel, K. Genome-wide association study to identify novel loci associated with therapy-related myeloid leukemia susceptibility. Blood. (2009). , 113(22), 5575-82.

[101] Knoche, E., Mc Leod, H. L., & Graubert, T. A. Pharmacogenetics of alkylator-associated acute myeloid leukemia. Pharmacogenomics. (2006). , 7(5), 719-29.

[102] Kobzev, Y. N., Martinez-Climent, J., Lee, S., Chen, J., & Rowley, . Analysis of translocations that involve the NUP98 gene in patients with 11chromosomal rearrangements. Genes Chromosomes Cancer. (2004)., 41(4), 339-52.

[103] Kolte, B., Baer, A. N., Sait, S. N., O'Loughlin, K. L., Stewart, C. C., Barcos, M., Wetzler, M., & Baer, M. R. Acute myeloid leukemia in the setting of low dose weekly methotrexate therapy for rheumatoid arthritis. Leuk Lymphoma. (2001). , 42(3), 371-8.

[104] Kosmider O, Delabesse E, de Mas VM, Cornillet-Lefebvre P, Blanchet O, Delmer A, Recher C, Raynaud S, Bouscary D, Viguié F, Lacombe C, Bernard OA, Ifrah N, Drey-

fus F, Fontenay M; GOELAMS Investigators. TET2 mutations in secondary acute myeloid leukemias: a French retrospective study. Haematologica. 2011;96(7):1059-63.

[105] Kristinsson SY, Björkholm M, Hultcrantz M, Derolf ÅR, Landgren O, Goldin LR.Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. J Clin Oncol. 2011;29(21):2897-903.

[106] Kratz CP, Emerling BM, Donovan S, Laig-Webster M, Taylor BR, Thompson P, Jensen S, Banerjee A, Bonifas J, Makalowski W, Green ED, Le Beau MM, Shannon KM.Candidate gene isolation and comparative analysis of a commonly deleted segment of 7q22 implicated in myeloid malignancies. Genomics. 2001;77(3):171-80.

[107] Kröger N, Brand R, van Biezen A, Zander A, Dierlamm J, Niederwieser D, Devergie A, Ruutu T, Cornish J, Ljungman P, Gratwohl A, Cordonnier C, Beelen D, Deconinck E, Symeonidis A, de Witte T; Myelodysplastic Syndromes Subcommittee of The Chronic Leukaemia Working Party of European Group for Blood and Marrow Transplantation (EBMT). Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic stem cell transplantation.Haematologica. 2009;94(4):542-9.

[108] Kuptsova-Clarkson N, Ambrosone CB, Weiss J, Baer MR, Sucheston LE, Zirpoli G, Kopecky KJ, Ford L, Blanco J, Wetzler M, Moysich KB. XPD DNA nucleotide excision repair gene polymorphisms associated with DNA repair deficiency predict better treatment outcomes in secondary acute myeloid leukemia. Int J Mol Epidemiol Genet. 2010;1(4):278-94.

[109] Kwong YL. Azathioprine: association with therapy-related myelodysplastic syndrome and acute myeloid leukemia.J Rheumatol. (2010). , 37(3), 485-90.

[110] Kyle RA, Pierre RV, Bayrd ED.Multiple myeloma and acute myelomonocytic leukemia. N Engl J Med. (1970). , 283(21), 1121-5.

[111] Lam DH, Aplan PD. NUP98 gene fusions in hematologic malignancies. Leukemia. 2001;15(11):1689-95.

[112] Larson RA, Le Beau MM.Prognosis and therapy when acute promyelocytic leukemia and other "good risk" acute myeloid leukemias occur as a therapy-related myeloid neoplasm. Mediterr J Hematol Infect Dis. (2011). e2011032.

[113] Larson RA. Therapy-related myeloid leukemia: stochastic or idiosyncratic? Blood,. (2004). 104, 602-603.

[114] Larson RA.Etiology and management of therapy-related myeloid leukemia. Hematology Am Soc Hematol Educ Program. (2007). , 2007, 453-9.

[115] Latagliata, R., Petti, M. C., Fenu, S., Mancini, M., Spiriti, Breccia. M., Brunetti, G. A., Avvisati, G., Lo, Coco. F., & Mandelli, F. Therapy-related myelodysplastic syndrome-acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem. Blood. (2002). , 99(3), 822-4.

[116] Le Beau, Espinosa. R., 3rd Davis, E. M., Eisenbart, Larson. R. A., & Green, E. D. Cytogenetic and molecular delineation of a region of chromosome 7 commonly deleted in malignant myeloid diseases. Blood. (1996). Sep 15;, 88(6), 1930-5.

[117] Le Beau MM, Olney HJ. Myelodysplastic Syndroms. In: Cancer Cytogenetics: Chromosomal and Molecular Genetic Abberations of Tumor Cells.Eds. Heim S, Mitelman F. 3rd ed.- Oxford : Wiley-Blackwell, (2009). , 141-178.

[118] Le Deley, M. C., Leblanc, T., Shamsaldin, A., Raquin, Lacour. B., Sommelet, D., Chompret, A., Cayuela, J. M., Bayle, C., Bernheim, A., de Vathaire, F., Vassal, G., Hill, C., Société, Française., & d'Oncologie, Pédiatrique. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Société Française d'Oncologie Pédiatrique. J Clin Oncol. (2003). , 21(6), 1074-81.

[119] Lee JW, Soung YH, Park WS, Kim SY, Nam SW, Min WS, Lee JY, Yoo NJ, Lee SH.BRAF mutations in acute leukemias.Leukemia. (2004). , 18(1), 170-2.

[120] Leone, G., Pagano, L., Ben-Yehuda, D., & Voso, M. T. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. (2007). , 92(10), 1389-98.

[121] Lenz, G., Dreyling, M., Schiegnitz, E., Haferlach, T., Hasford, J., Unterhalt, M., & Hiddemann, W. Moderate increase of secondary hematologic malignancies after myeloablative radiochemotherapy and autologous stem-cell transplantation in patients with indolent lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group. J Clin Oncol. (2004). , 22(24), 4926-33.

[122] Leone, G., Pagano, L., Ben-Yehuda, D., & Voso, M. T. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. (2007). , 92(10), 1389-98.

[123] Leone G, Pagano L, Ben-Yehuda D, Voso MT. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. 2007;92(10):1389-98.

[124] Li, L., Li, M., Sun, C., Francisco, L., Chakraborty, S., Sabado, M., Mc Donald, T., Gyorffy, J., Chang, K., Wang, S., Fan, W., Li, J., Zhao, L. P., Radich, J., Forman, S., Bhatia, S., & Bhatia, R. Altered hematopoietic cell gene expression precedes development of therapy-related myelodysplasia/acute myeloid leukemia and identifies patients at risk. Cancer Cell. (2011). , 20(5), 591-605.

[125] Lichtman MA.Is there an entity of chemically induced BCR-ABL-positive chronic myelogenous leukemia? Oncologist. (2008)., 13(6), 645-54.

[126] Lin LI, Chen CY, Lin DT, Tsay W, Tang JL, Yeh YC, Shen HL, Su FH, Yao M, Huang SY, Tien HF. Characterization of CEBPA mutations in acute myeloid leukemia: most patients with CEBPA mutations have biallelic mutations and show a distinct immunophenotype of the leukemic cells. Clin Cancer Res. 2005;11(4):1372-9.

[127] Litzow, M. R., Tarima, S., Pérez, W. S., Bolwell, B. J., Cairo, Camitta., Cutler, C. S., de Lima, M., Dipersio, J. F., Gale, R. P., Keating, A., Lazarus, H. M., Luger, S., Marks, D. I., Maziarz, R. T., Mc Carthy, P. L., Pasquini, M. C., Phillips, G. L., Rizzo, Sierra. J., & Tallman, Weisdorf. D. J. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia.Blood.(2010). , 115(9), 1850-7.

[128] Lofstrom, B., Backlin, C., Sundstrom, C., Hellstrom-Lindberg, E., Ekbom, A., & Lundberg, I. E. Myeloid leukaemia in systemic lupus erythematosus--a nested case-control study based on Swedish registers.Rheumatology (Oxford) (2009). , 48(10), 1222-6.

[129] Lyman, G. H., Dale, D. C., Wolff, D. A., Culakova, E., Poniewierski, Kuderer. N. M., & Crawford, J. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol. (2010). Jun 10;, 28(17), 2914-24.

[130] Luna-Fineman S, Shannon KM, Lange BJ. Childhood monosomy 7: epidemiology,biology, and mechanistic implications. Blood. 1995;85(8):1985-99.

[131] Mailankody, S., Pfeiffer, R. M., Kristinsson, S. Y., Korde, N., Bjorkholm, M., Goldin, L. R., Turesson, I., & Landgren, O. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). Blood. (2011). , 118(15), 4086-92.

[132] Marcucci G, Maharry K, Wu YZ, Radmacher MD, Mrózek K, Margeson D, Holland KB, Whitman SP, Becker H, Schwind S, Metzeler KH, Powell BL, Carter TH, Kolitz JE, Wetzler M, Carroll AJ, Baer MR, Caligiuri MA, Larson RA, Bloomfield CD. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol. 2010;28(14):2348-55.

[133] Maris JM, Wiersma SR, Mahgoub N, Thompson P, Geyer RJ, Hurwitz CG, Lange BJ,Shannon KM. Monosomy 7 myelodysplastic syndrome and other second malignant neoplasms in children with neurofibromatosis type 1. Cancer. 1997;79(7): 1438-46.

[134] Martin, M. G., Welch, J. S., Luo, J., Ellis, Graubert. T. A., & Walter, . Therapy related acute myeloid leukemia in breast cancer survivors, a population-based study. Breast Cancer Res Treat. (2009). , 118(3), 593-8.

[135] Martinelli V, Radaelli M, Straffi L, Rodegher M, Comi G. Mitoxantrone: benefits and risks in multiple sclerosis patients. Neurol Sci. 2009;30(Suppl 2):S167–70

[136] Mauch, P. M., Kalish, L. A., Marcus, K. C., Coleman, C. N., Shulman, L. N., Krill, E., Come, S., Silver, B., Canellos, G. P., & Tarbell, N. J. Second malignancies after treatment for laparotomy staged IA-IIIB Hodgkin's disease: long-term analysis of risk factors and outcome. Blood. (1996). , 87(9), 3625-32.

[137] Mauritzson, N., Albin, M., Rylander, L., et al. Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and

myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia. (2002). , 16(12), 2366-78.

[138] Mays, A. N., Osheroff, N., Xiao, Y., Wiemels, J. L., Felix, Byl. J. A., Saravanamuttu, K., Peniket, A., Corser, R., Chang, C., Hoyle, C., Parker, A. N., Hasan, S. K., Lo-Coco, F., Solomon, E., & Grimwade, D. Evidence for direct involvement of epirubicin in the formation of chromosomal translocations in t(15;17) therapy-related acute promyelocytic leukemia. Blood. (2010). , 115(2), 326-30.

[139] Metayer, C., Curtis, R. E., Vose, J., Sobocinski, K. A., Horowitz, Bhatia. S., Fay, J. W., Freytes, C. O., Goldstein, S. C., Herzig, R. H., Keating, A., Miller, C. B., Nevill, T. J., Pecora, A. L., Rizzo, Williams. S. F., Li, C. Y., Travis, L. B., & Weisdorf, D. J. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study. Blood. (2003). , 101(5), 2015-23.

[140] Micallef, I. N., Lillington, D. M., Apostolidis, J., Amess, J. A., Neat, M., Matthews, J., Clark, T., Foran, J. M., Salam, A., Lister, T. A., & Rohatiner, A. Z. Therapy-related myelodysplasia and secondary acute myelogenous leukemia after high-dose therapy with autologous hematopoietic progenitor-cell support for lymphoid malignancies. J Clin Oncol. (2000). , 18(5), 947-55.

[141] Mistry AR, Felix CA, Whitmarsh RJ, Mason A, Reiter A, Cassinat B, Parry A, Walz C, Wiemels JL, Segal MR, Adès L, Blair IA, Osheroff N, Peniket AJ,Lafage-Pochitaloff M, Cross NC, Chomienne C, Solomon E, Fenaux P, Grimwade D. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. N Engl J Med. 2005;352(15): 1529-38.

[142] Miyata A, Deguchi S, Fujita M, Kikuchi T, Honda K. [Therapy-related AML(M2) with t(8;21) that developed three years after chemo-therapy for hepatocellular carcinoma]. Rinsho Ketsueki. 1996;37(5):448-51.

[143] Morrison, V. A., Rai, K. R., Peterson, B. L., Kolitz, J. E., Elias, L., Appelbaum, F. R., Hines, Shepherd. L., Larson, R. A., & Schiffer, . Therapy-related myeloid leukemias are observed in patients with chronic lymphocytic leukemia after treatment with fludarabine and chlorambucil: results of an intergroup study, cancer and leukemia group B 9011. J Clin Oncol. (2002). , 20(18), 3878-84.

[144] Mudie, N. Y., Swerdlow, A. J., Higgins, C. D., Smith, P., Qiao, Z., Hancock, B. W., Hoskin, P. J., & Linch, D. C. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. J Clin Oncol. (2006). , 24(10), 1568-74.

[145] Nakamori, Y., Miyazaki, M., Tominaga, T., Taguchi, A., & Shinohara, K. Therapy-related erythroleukemia caused by the administration of UFT and mitomycin C in a patient with colon cancer. Int J Clin Oncol. (2003). , 8(1), 56-9.

[146] Nardi, V., Winkfield, K. M., Ok, C. Y., Niemierko, A., Kluk, Attar. E. C., Garcia-Manero, G., Wang, S. A., & Hasserjian, R. P. Acute myeloid leukemia and myelodysplas-

tic syndromes after radiation therapy are similar to de novo disease and differ from other therapy-related myeloid neoplasms. J Clin Oncol. (2012). , 30(19), 2340-7.

[147] Nishiyama M, Arai Y, Tsunematsu Y, Kobayashi H, Asami K, Yabe M, Kato S, Oda M, Eguchi H, Ohki M, Kaneko Y. 11p15 translocations involving the NUP98 gene in childhood therapy-related acute myeloid leukemia/myelodysplastic syndrome. Genes Chromosomes Cancer. 1999;26(3):215-20.

[148] Noronha V, Berliner N, Ballen KK, Lacy J, Kracher J, Baehring J, Henson JW. Treatment-related myelodysplasia/AML in a patient with a history of breast cancer and an oligodendroglioma treated with temozolomide: case study and review of the literature. Neuro Oncol. 2006;8(3):280-3.

[149] Offman J, Opelz G, Doehler B, Cummins D, Halil O, Banner NR, Burke MM, Sullivan D, Macpherson P, Karran P. Defective DNA mismatch repair in acute myeloid leukemia/myelodysplastic syndrome after organ transplantation. Blood. 2004;104(3):822-8.

[150] Ojha, R. P., Fischbach, L. A., Zhou, Y., Felini, Singh. K. P., & Thertulien, R. Acute myeloid leukemia incidence following radiation therapy for localized or locally advanced prostate adenocarcinoma.Cancer Epidemiol. (2010). , 34(3), 274-8.

[151] Osato, M. Point mutations in the RUNX1/AML1 gene: another actor in RUNX leukemia. Oncogene. (2004). , 23(24), 4284-96.

[152] Ostgård, L. S., Kjeldsen, E., Holm, Brown., Pde, N., Pedersen, B. B., Bendix, K., Johansen, P., Kristensen, J. S., & Nørgaard, J. M. Reasons for treating secondary AML as de novo AML. Eur J Haematol. (2010). , 85(3), 217-26.

[153] Pagano, L., Pulsoni, A., Tosti, Avvisati. G., Mele, L., Mele, M., Martino, B., Visani, G., Cerri, R., Di Bona, E., Invernizzi, R., Nosari, A., Clavio, M., Allione, B., Coser, P., Candoni, A., Levis, A., Camera, A., Melillo, L., Leone, G., Mandelli, F., Gruppo, Italiano., Malattie, Ematologiche., & Maligne, dell'Adulto. Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. Br J Haematol. (2001). , 112(1), 109-17.

[154] Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Krönke J, Bullinger L, Späth D, Kayser S, Zucknick M, Götze K, Horst HA, Germing U, Döhner H, Döhner K. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol. 2010;28(22): 3636-43.

[155] Patel, J. P., Gönen, M., Figueroa, Fernandez. H., Sun, Z., Racevskis, J., Van Vlierberghe, P., Dolgalev, I., Thomas, S., Aminova, O., Huberman, K., Cheng, J., Viale, A., Socci, N. D., Heguy, A., Cherry, A., Vance, G., Higgins, R. R., Ketterling, R. P., Gallagher, R. E., Litzow, M., van den, Brink. M. R., Lazarus, H. M., Rowe, J. M., Luger, S., Ferrando, A., Paietta, E., Tallman, Melnick. A., Abdel-Wahab, O., & Levine, R. L. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. (2012). , 366(12), 1079-89.

[156] Pedersen-Bjergaard, J. Insights into leukemogenesis from therapy-related leukemia. N Engl J Med. (2005). , 352(15), 1591-4.

[157] Pedersen-Bjergaard, J., Andersen, M. K., Andersen, M. T., & Christiansen, D. H. Genetics of therapy-related myelodysplasia and acute myeloid leukemia.Leukemia. (2008). , 22(2), 240-8.

[158] Pedersen-Bjergaard, J., Andersen, M. T., & Andersen, M. K. Genetic pathways in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia.Hematology Am Soc Hematol Educ Program.(2007). , 2007, 392-7.

[159] Pedersen-Bjergaard, J., Christiansen, D. H., Desta, F., & Andersen, M. K. Alternative genetic pathways and cooperating genetic abnormalities in the pathogenesis of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia. (2006). , 20(11), 1943-9.

[160] Pedersen-Bjergaard, J., Daugaard, G., Hansen, S. W., Philip, P., Larsen, S. O., & Rørth, M. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. Lancet. (1991). , 338(8763), 359-63.

[161] Pedersen-Bjergaard, J., Nissen, N. I., Sørensen, H. M., Hou-Jensen, K., Larsen, Ernst. P., Ersbøl, J., Knudtzon, S., & Rose, C. Acute non-lymphocytic leukemia in patients with ovarian carcinoma following long-term treatment with Treosulfan (=dihydroxybusulfan). Cancer. (1980). , 45(1), 19-29.

[162] Pedersen-Bjergaard, J. Molecular cytogenetics in cancer.Lancet. (2001). , 357(9255), 491-2.

[163] Perentesis JP.Genetic predisposition and treatment-related leukemia.Med Pediatr Oncol. (2001). , 36(5), 541-8.

[164] Perry JR, Brown MT, Gockerman JP.Acute leukemia following treatment of malignant glioma.J Neurooncol. 1998;40(1):39-46.

[165] Praga, C., Bergh, J., Bliss, J., Bonneterre, J., Cesana, B., Coombes, R. C., Fargeot, P., Folin, A., Fumoleau, P., Giuliani, R., Kerbrat, P., Hery, M., Nilsson, J., Onida, F., Piccart, M., Shepherd, L., Therasse, P., Wils, J., & Rogers, D. Risk of acute myeloid leukemia and myelodysplastic syndrome in trials of adjuvant epirubicin for early breast cancer: correlation with doses of epirubicin and cyclophosphamide. J Clin Oncol. (2005). , 23(18), 4179-91.

[166] Preudhomme, C., Sagot, C., Boissel, N., Cayuela, J. M., Tigaud, I., de Botton, S., Thomas, X., Raffoux, E., Lamandin, C., Castaigne, S., Fenaux, P., Dombret, H., & Group, A. L. F. A. Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). Blood. (2002). , 100(8), 2717-23.

[167] Pui-H, C., Behm, F. G., Raimondi, S. C., Dodge, R. K., George, S. L., Rivera, G. K., Mirro, J., Kalwinsky, D. K., Dahl, G. V., Murphy, S. B., Crist, W. M., & Williams, D. L.

Secondary Acute Myeloid Leukemia in Children Treated for Acute Lymphoid Leukemia. N Engl J Med (1989)., 321(3), 136-142.

[168] Pyatt DW, Aylward LL, Hays SM.Is age an independent risk factor for chemically induced acute myelogenous leukemia in children?J Toxicol Environ Health B Crit Rev. 2007;10(5):379-400

[169] Qian, Z., Fernald, Godley. L. A., Larson, R. A., & Le Beau, . Expression profiling of CD34+ hematopoietic stem/ progenitor cells reveals distinct subtypes of therapy-related acute myeloid leukemia. Proc Natl Acad Sci U S A. (2002). , 99(23), 14925-30.

[170] Qian, Z., Joslin, J. M., Tennant, T. R., Reshmi, S. C., Young, D. J., Stoddart, A., Larson, R. A., & Le Beau, . Cytogenetic and genetic pathways in therapy-related acute myeloid leukemia.Chem Biol Interact. (2010)., 184(1-2), 50-7.

[171] Quesnel, B., Kantarjian, H., Bjergaard, J. P., Brault, P., Estey, E., Lai, J. L., Tilly, H., Stoppa, A. M., Archimbaud, E., Harousseau, J. L., et al. Therapy-related acute myeloid leukemia with t(8;21), inv(16), and t(8;16): a report on 25 cases and review of the literature. J Clin Oncol. (1993). , 11(12), 2370-9.

[172] Ramadan, S. M., Fouad, T. M., Summa, V., Hasan, S., Kh-Coco, Lo., & , F. Acute myeloid leukemia developing in patients with autoimmune diseases. Haematologica. (2012). , 97(6), 805-17.

[173] Rassool FV, Gaymes TJ, Omidvar N, Brady N, Beurlet S, Pla M, Reboul M, Lea N, Chomienne C, Thomas NS, Mufti GJ, Padua RA. Reactive oxygen species, DNA damage, and error-prone repair: a model for genomic instability with progression in myeloid leukemia? Cancer Res. 2007;67(18):8762-71.

[174] Relling, M. V., Boyett, J. M., Blanco, J. G., Raimondi, S., Behm, F. G., Sandlund, J. T., Rivera, G. K., Kun, L. E., Evans, W. E., & Pui, C. H. Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. Blood. (2003). , 101(10), 3862-7.

[175] Ries LAG, Harkins D, Krapcho M, et al. SEER cancer statistics review, 1975-2003. Based on November 2005 SEER data submission. Bethesda, Md: National Cancer Institute; 2006. Available at: http://seer.cancer.gov/csr/1975_2003 Accessed October 7, 2008.

[176] Riggi M, Riva A. Therapy-related leukemia: what is the role of 4-epidoxorubicin? J Clin Oncol. 1993;11(7):1430-1.

[177] Rosenthal NS, Farhi DC.Myelodys-plastic syndromes and acute myeloid leukemia in connective tissue disease after single-agent chemotherapy.Am J Clin Pathol. 1996;106(5):676-9.

[178] Rund, D., & Ben-Yehuda, D. Therapy-related leukemia and myelodysplasia: evolving concepts of pathogenesis and treatment. Hematology. (2004). , 9(3), 179-87.

[179] Rund D, Krichevsky S, Bar-Cohen S, Goldschmidt N, Kedmi M, Malik E, Gural A,Shafran-Tikva S, Ben-Neriah S, Ben-Yehuda D. Therapy-related leukemia: clinical

characteristics and analysis of new molecular risk factors in 96 adult patients. Leukemia. 2005;19(11):1919-28.

[180] Sakai I, Tamura T, Narumi H, Uchida N, Yakushijin Y, Hato T, Fujita S,Yasukawa M. Novel RUNX1-PRDM16 fusion transcripts in a patient with acute myeloid leukemia showing t(1;21)(p36;q22). Genes Chromosomes Cancer. 2005;44(3):265-70.

[181] Salas, C., Pérez-Vera, P., & Frías, S. Genetic abnormalities in leukemia secondary to treatment in patients with Hodgkin's disease. Rev Invest Clin. (2011). , 63(1), 53-63.

[182] Sala-Torra, O., Hanna, C., Loken, M. R., Flowers, Maris. M., Ladne, P. A., Mason, J. R., Senitzer, D., Rodriguez, R., Forman, S. J., Deeg, H. J., & Radich, J. P. Evidence of donor-derived hematologic malignancies after hematopoietic stem cell transplantation.Biol Blood Marrow Transplant. (2006). , 12(5), 511-7.

[183] Samanta, D. R., Senapati, S. N., Sharma, P. K., Mohanty, A., & Samantaray, S. Acute myelogenous leukemia following treatment of invasive cervix carcinoma: a case report and a review of the literature. J Cancer Res Ther. (2009). , 5(4), 302-4.

[184] Sandoval C, Head DR, Mirro J Jr, Behm FG, Ayers GD, Raimondi SC. Translocation (9;11)(p21;q23) in pediatric de novo and secondary acute myeloblastic leukemia. Leukemia. 1992;6(6):513-9

[185] Scaradavou, A., Heller, G., Sklar, Ren. L., & Ghavimi, F. Second malignant neoplasms in long-term survivors of childhood rhabdomyosarcoma. Cancer. (1995). , 76(10), 1860-7.

[186] Schaich, M., Ritter, M., Illmer, T., Lisske, P., Thiede, C., Schäkel, U., Mohr, B., Ehninger, G., & Neubauer, A. Mutations in ras proto-oncogenes are associated with lower mdr1 gene expression in adult acute myeloid leukaemia. Br J Haematol. (2001). , 112(2), 300-7.

[187] Schneider, D. T., Hilgenfeld, E., Schwabe, D., Behnisch, W., Zoubek, A., Wessalowski, R., & Göbel, U. Acute myelogenous leukemia after treatment for malignant germ cell tumors in children. J Clin Oncol. (1999). , 17(10), 3226-33.

[188] Schnittger S, Bacher U, Haferlach C, Kern W, Haferlach T. Rare CBFB-MYH11 fusion transcripts in AML with inv(16)/t(16;16) are associated with therapy-related AML M4eo, atypical cytomorphology, atypical immunophenotype, atypical additional chromosomal rearrangements and low white blood cell count: a study on 162 patients. Leukemia. 2007;21(4):725-31.

[189] Schoch C, Schnittger S, Klaus M, Kern W, Hiddemann W, Haferlach T. AML with 11q23/MLL abnormalities as defined by the WHO classification: incidence, partner chromosomes, FAB subtype, age distribution, and prognostic impact in an unselected series of 1897 cytogenetically analyzed AML cases. Blood. 2003;102(7):2395-40

[190] Schoch, C., Kern, W., Schnittger, S., Hiddemann, W., & Haferlach, T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-

AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia.(2004). , 18(1), 120-5.

[191] See, H. T., Thomas, D. A., Bueso-Ramos, C., & Kavanagh, J. Secondary leukemia after treatment with paclitaxel and carboplatin in a patient with recurrent ovarian cancer. Int J Gynecol Cancer. (2006)., 16(Suppl 1), 236-40.

[192] Seedhouse, C., Bainton, R., Lewis, M., Harding, A., Russell, N., & Das-Gupta, E. The genotype distribution of the XRCC1 gene indicates a role for base excision repair in the development of therapy-related acute myeloblastic leukemia. Blood. (2002). , 100(10), 3761-6.

[193] Seedhouse, C., Faulkner, R., Ashraf, N., Das-Gupta, E., & Russell, N. Polymorphisms in genes involved in homologous recombination repair interact to increase the risk of developing acute myeloid leukemia. Clin Cancer Res. (2004). , 10(8), 2675-80.

[194] Seedhouse, C., & Russell, N. Advances in the understanding of susceptibility to treatment-related acute myeloid leukaemia. Br J Haematol. (2007). , 137(6), 513-29.

[195] Shen, Y., Zhu, Y. M., Fan, X., Shi, J. Y., Wang, Q. R., Yan, X. J., Gu, Z. H., Wang, Y. Y., Chen, B., Jiang, C. L., Yan, H., Chen, F. F., Chen, H. M., Chen, Z., Jin, J., & Chen, S. J. Gene mutation patterns and their prognostic impact in a cohort of 1185 patients with acute myeloid leukemia.Blood. (2011). , 118(20), 5593-603.

[196] Sill, H., Olipitz, W., Zebisch, A., Schulz, E., Wölfler, A., Therapy-related, myeloid., neoplasms, pathobiology., & clinical, characteristics. Br J Pharmacol. (2011). , 162(4), 792-805.

[197] Slovak ML, Bedell V, Popplewell L, Arber DA, Schoch C, Slater R. 21q22 balanced chromosome aberrations in therapy-related hematopoietic disorders: report from an international workshop. Genes Chromosomes Cancer. 2002;33(4):379-94.

[198] Smit, C. G., & Meyler, L. Acute myeloid leukaemia after treatment with cytostatic agents. Lancet. (1970). , 2(7674), 671-2.

[199] Smith, M. R., Neuberg, D., Flinn, I. W., Grever, M. R., Lazarus, H. M., Rowe, J. M., Dewald, G., Bennett, J. M., Paietta, E. M., Byrd, J. C., Hussein, Appelbaum. F. R., Larson, R. A., Litzow, M. R., & Tallman, . Incidence of therapy-related myeloid neoplasia after initial therapy for chronic lymphocytic leukemia with fludarabine-cyclophosphamide versus fludarabine: long-term follow-up of US Intergroup Study E2997. Blood. (2011). , 118(13), 3525-7.

[200] Smith, S. M., Le Beau, Huo. D., Karrison, T., Sobecks, R. M., Anastasi, J., Vardiman, J. W., & Rowley, Larson. R. A. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood. (2003). , 102(1), 43-52.

[201] Spina, F., Alessandrino, P. E., Milani, R., Bonifazi, F., Bernardi, M., Luksch, R., Fagioli, F., Formica, C., & Farina, L. Allogeneic stem cell transplantation in therapy-related

acute myeloid leukemia and myelodysplastic syndromes: impact of patient characteristics and timing of transplant. Leuk Lymphoma. (2012). , 53(1), 96-102.

[202] Stavropoulou, V., Brault, L., & Schwaller, J. Insights into molecular pathways for targeted therapeutics in acute leukemia. Swiss Med Wkly. (2010). w13068.

[203] Suvajdžić, N., Cvetković, Z., Dorđević, V., Kraguljac-Kurtović, N., Stanisavljević, D., Bogdanović, A., Djunić, I., Colović, N., Vidović, A., Elezović, I., & Tomin, D. Prognostic factors for therapy-related acute myeloid leukaemia (t-AML)- A single centre experience. Biomed Pharmacother. (2012). , 66(4), 285-92.

[204] Takahashi, T., Yamamoto, R., Tanaka, K., Kamada, N., & Miyagawa, K. Mutation analysis of the WT1 gene in secondary leukemia. Leukemia. (2000). , 14(7), 1316-7.

[205] Talwalkar SS, Yin CC, Naeem RC, Hicks MJ, Strong LC, Abruzzo LV.Myelodysplastic syndromes arising in patients with germline TP53 mutation and Li-Fraumeni syndrome. Arch Pathol Lab Med. (2010). , 134(7), 1010-5.

[206] Tarella, C., Passera, R., Magni, M., Benedetti, F., Rossi, A., Gueli, A., Patti, C., Parvis, G., Ciceri, F., Gallamini, A., Cortelazzo, S., Zoli, V., Corradini, P., Carobbio, A., Mulé, A., Bosa, M., Barbui, A., Di Nicola, M., Sorio, M., Caracciolo, D., Gianni, A. M., & Rambaldi, A. Risk factors for the development of secondary malignancy after high-dose chemotherapyand autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol. (2011). , 29(7), 814-24.

[207] Tavernier, E., Le de Botton, Q. H., Dhédin, S., Bulabois, N., Reman, O., Vey, N., Lhéritier, V., Dombret, H., & Thomas, X. Secondary or concomitant neoplasms among adults diagnosed with acute lymphoblastic leukemia and treated according to the LALA-87 and LALA-94 trials. Cancer. (2007). , 110(12), 2747-55.

[208] Thiede, C., Steudel, C., Mohr, B., Schaich, M., Schäkel, U., Platzbecker, U., Wermke, M., Bornhäuser, M., Ritter, M., Neubauer, A., Ehninger, G., & Illmer, T. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood. (2002). , 99(12), 4326-35.

[209] Touw IP, Bontenbal M. Granulocyte colony-stimulating factor: key (f)actor or innocent bystander in the development of secondary myeloid malignancy?J Natl Cancer Inst. 2007;99(3):183-6.

[210] Travis, L. B., Andersson, M., Gospodarowicz, M., van Leeuwen, F. E., Bergfeldt, K., Lynch, C. F., Curtis, R. E., Kohler, Wiklund. T., Storm, H., Holowaty, E., Hall, P., Pukkala, E., Sleijfer, D. T., Clarke, E. A., Boice Jr, Stovall. M., & Gilbert, E. Treatment-associated leukemia following testicular cancer. J Natl Cancer Inst. (2000). , 92(14), 1165-71.

[211] Travis LB, Curtis RE, Boice JD Jr, Hankey BF, Fraumeni JF Jr.Second cancers following non-Hodgkin's lymphoma.Cancer. (1991). , 67(7), 2002-9.

[212] Travis, L. B., Curtis, R. E., Storm, H., Hall, P., Holowaty, E., Van Leeuwen, F. E., Kohler, Pukkala. E., Lynch, C. F., Andersson, M., Bergfeldt, K., Clarke, E. A., Wiklund, T., Stoter, G., Gospodarowicz, M., Sturgeon, J., Fraumeni, J. F., & Jr Boice Jr, . Risk of second malignant neoplasms among long-term survivors of testicular cancer. J Natl Cancer Inst. (1997). , 89(19), 1429-39.

[213] Travis, L. B., Curtis, R. E., Stovall, M., Holowaty, E. J., van Leeuwen, F. E., Glimelius, B., Lynch, C. F., Hagenbeek, A., Li, C. Y., Banks, P. M., et al. Risk of leukemia following treatment for non-Hodgkin's lymphoma. J Natl Cancer Inst. (1994). , 86(19), 1450-7.

[214] Travis, L. B., Holowaty, E. J., Bergfeldt, K., Lynch, C. F., Kohler, Wiklund. T., Curtis, R. E., Hall, P., Andersson, M., Pukkala, E., Sturgeon, J., & Stovall, M. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med. (1999). , 340(5), 351-7.

[215] Travis, L. B., Weeks, J., Curtis, R. E., Chaffey, J. T., Stovall, M., Banks, P. M., & Boice Jr, . Leukemia following low-dose total body irradiation and chemotherapy for non-Hodgkin's lymphoma. J Clin Oncol. (1996). , 14(2), 565-71.

[216] Travis LB.The epidemiology of second primary cancers. Cancer Epidemiol Biomarkers Prev (2006). , 15(11), 2020-6.

[217] Trumpp, A., Essers, M., & Wilson, A. Awakening dormant haematopoietic stem cells.Nat Rev Immunol. (2010). , 10(3), 201-9.

[218] Turker, A., & Güler, N. Therapy related acute myeloid leukemia after exposure to 5-fluorouracil: a case report. Hematol Cell Ther. (1999). , 41(5), 195-6.

[219] United National Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). UNSCEAR 2000 Report to General Assembly, with scientific annexes, sources, and effects of ionizing radiation. New York: United Nations; (2000).

[220] van Leeuwen, F. E., Stiggelbout, A. M., van den-Dusebout, Belt., Noyon, A. W., Eliel, R., R,van, M., Kerkhoff, E. H., Delemarre, J. F., & Somers, R. Second cancer risk following testicular cancer: a follow-up study of 1,909 patients. J Clin Oncol. (1993). , 11(3), 415-24.

[221] Vardiman J, Arber DA, Brunning RD, et al. Therapy-related myeloid neoplasms. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (eds S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.a. Pileri, H. Stein, J. thiele & J.W. Vardiman), 2008, pp. 127-129.IARC, Lyon.

[222] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellström-Lindberg E, Tefferi A, Bloomfield CD. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-51.

[223] Vay, A., Kumar, S., Seward, S., Semaan, A., Schiffer, Munkarah. A. R., & Morris, R. T. Therapy-related myeloid leukemia after treatment for epithelial ovarian carcinoma: an epidemiological analysis. Gynecol Oncol. (2011). , 123(3), 456-60.

[224] Verma, D., O'Brien, S., Thomas, D., Faderl, S., Koller, C., Pierce, S., Kebriaei, P., Garcia-Manero, G., Cortes, J., Kantarjian, H., & Ravandi, F. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome in patients with acute lymphoblastic leukemia treated with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens. Cancer. (2009). , 115(1), 101-6.

[225] Voso, M. T., D'Alò, F., Greco, M., Fabiani, E., Criscuolo, M., Migliara, G., Pagano, L., Fianchi, L., Guidi, F., Hohaus, S., & Leone, G. Epigenetic changes in therapy-related MDS/AML. Chem Biol Interact. (2010).

[226] Wang, E., Hutchinson, C. B., Huang, Q., Lu, C. M., Crow, J., Wang, F. F., Sebastian, S., Rehder, C., Lagoo, A., Horwitz, M., Rizzieri, D., Yu, J., Goodman, B., Datto, M., & Buckley, P. Donor cell-derived leukemias/myelodysplastic neoplasms in allogeneic hematopoietic stem cell transplant recipients: a clinicopathologic study of 10 cases and a comprehensive review of the literature. Am J Clin Pathol. (2011). , 135(4), 525-40.

[227] Westman MK, Andersen MT, Pedersen-Bjergaard J, Andersen MK. IDH1 and IDH2 Mutations in Therapy-Related Acute Myeloid Leukemia Are Associated with a Normal Karyotype or Der(1;7)(q10;p10) Combined with RUNX1 Mutations. Blood (ASH Annual Meeting Abstracts), 2011, abstact 3514

[228] Wood BL. Myeloid malignancies: myelodysplastic syndromes, myeloproliferative disorders, and acute myeloid leukemia.Clin Lab Med. (2007). , 27(3), 551-75.

[229] Xue Y, Guo Y, Xie X. Translocation t(7;11)(P15;P15) in a patient with therapy-related acute myeloid leukemia following bimolane and ICRF-154 treatment for psoriasis. Leuk Res. 1997;21(2):107-9.

[230] Yang, J., Terebelo, H. R., & Zonder, J. A. Secondary Primary Malignancies in Multiple Myeloma: An Old Nemesis Revisited. Adv Hematol. (2012)., 2012:801495.

[231] Yin CC, Glassman AB, Lin P, Valbuena JR, Jones D, Luthra R, Medeiros LJ. Morphologic, cytogenetic, and molecular abnormalities in therapy-related acute promyelocytic leukemia.Am J Clin Pathol. 2005;123(6):840-8.

[232] Yonal, I., Hindilerden, F., Ozcan, E., Palanduz, S., & Aktan, M. The co-presence of deletion 7q, 20q and inversion 16 in therapy-related acute myeloid leukemia developed secondary to treatment of breast cancer with cyclophosphamide, doxorubicin, and radiotherapy: a case report. J Med Case Rep. (2012)., 6:67.

[233] Zhang, Y., & Rowley, . Chromatin structural elements and chromosomal translocations in leukemia. DNA Repair (Amst). (2006)., 5(9-10), 1282-97.

[234] Zhang Y, Wong J, Klinger M, Tran MT, Shannon KM, Killeen N. MLL5 contributes to hematopoietic stem cell fitness and homeostasis. Blood. 2009;113(7):1455-63.

[235] Zebisch A, Haller M, Hiden K, Goebel T, Hoefler G, Troppmair J, Sill H. Loss of RAF kinase inhibitor protein is a somatic event in the pathogenesis of therapy-related acute myeloid leukemias with C-RAF germline mutations. Leukemia. 2009;23(6): 1049-53.

IntechOpen

IntechOpen