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Therapy of Acute Myeloid Leukemia

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1. Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults[1]. Over the past twenty years, the studies on the pathogenesis and prognosis of AML have made considerable progress.

Clinically, patients with AML typically present with signs or symptoms of bone marrow failure, although sometimes they can present with symptoms of leukostasis with pulmonary or neurological dysfunction. Rarely, patients will present with primary extramedullary disease, which should be approached in the same way as systemic AML.

A certain number of factors can be involved in the etiology of AML: as an example, exposure to ionizing radiation and long-term exposure to benzene are known risk factors. AML could be part of the natural history of patients with congenital disorders of DNA repair, such as the Fanconi's anemias; also the myeloproliferative disorders (MPD) and myelodysplastic syndromes (MDS).

AML is a heterogeneous disease; standard treatments may be applied to biologically distinct subgroups, resulting in different treatment outcomes. However, less than one-third of all adult patients with AML can be cured even to this date. The treatment of refractory, relapsed and elderly AML remains a major challenge. In recent years, new regimens and novel agents are being studied in an effort to improve complete remission (CR) rate and overall survival. The concept of risk-adapted therapy allows for recognition of this biologic diversity by incorporating key biologic features, such as cytogenetic and molecular markers, when formulating treatment regimens and investigating emerging targeted therapies based on disease characteristics. Although AML has been the focus of significant laboratory and clinical investigation, it remains difficult to treat, perhaps partly because of the fundamental nature of the disorder, which requires substantial institutional resources to adequately deal with the complications of bone marrow failure and sustain patients through periods of intensive therapy. Several large studies have helped categorize chromosomal abnormalities into good-, intermediate-, and poor-risk groups[2-5]. This hierarchical system of karyotype classification is predictive value across different age groups in de novo and secondary AML. It was also found to retain prognostic significance across the different treatment modalities of chemotherapy and autologous and allogeneic bone marrow transplantation. Generally, the poor-risk or unfavorable group includes those with complex karyotypes (> 3-5 abnormalities), chromosome 5 or 7 abnormalities, or chromosome 3q abnormalities. The results for these patients are dismal, with standard chemotherapy causing some to advocate

patients undergoing stem cell transplantation in first remission[3,5]. In contrast, such an "aggressive" approach as allogeneic stem cell transplantation in first complete remission (CR) is generally not recommended in patients with good-risk or favorable cytogenetics. Included in this category are those with t(15;17), t(8;21), t(16;16), and inv(16) translocations[6]. Acute promyelocytic leukemia (APL), defined by the t(15;17) translocation, has a distinct biology, and combinations of dose-intensive anthracyclines, all-*trans*-retinoic acid (ATRA), and arsenic trioxide may be curative for most patients.

Age was not, however, found to be the only significant factor affecting treatment outcomes. Although supportive measures have generally improved within the past 20 years, the drugs that form the backbone of standard AML chemotherapy remain essentially unchanged.

2. Therapy

2.1 High dose daunorubicin

The standard induction regimen for newly diagnosed AML consists of daunorubicin (DNR) 45 mg/m^2 intravenously for 3 days and cytarabine (AraC) 100 mg/m^2 by continuous infusion for 7 days. With this regimen 60% to 80% of young adults and 40% to 60% of older adults can achieve a CR[7].

Several major studies, particularly Cancer and Leukemia Group B (CALGB) 9621 and the French ALFA 9801 studies, have shown that higher doses of DNR (80 or 90 mg/m^2) can be administered safely[8,9]. Recently, there are two major prospective studies compared DNR 90 mg/m^2 with 45 mg/m^2 in the induction regimen[10,11]. Eastern Cooperative Oncology Group (ECOG) studied 657 AML patients between the age of 17 to 60[10]. The study showed significantly higher CR rate for patients receiving 90 mg/m^2 (70% versus 57%). More importantly, overall survival (OS) was significantly prolonged (23.7 vs 15.7 months). The Dutch-Belgium Hemato-Oncology Cooperative Group (HOVON)/Swiss Group for Clinical Cancer Research (SAKK) compared DNR 90 mg/m^2 versus 45 mg/m^2 in 813 patients older than 60 years[11]. The results showed that CR rate was 64% and 54% respectively, while CR rate after only one course of treatment was 52% and 35% respectively. The OS rate was not significantly different for the whole group. However, for the patients between the age of 60 to 65, the OS rate was significantly better in the high dose group (38% vs 23%). The rates of serious adverse events were similar in the two treatment groups in both studies.

Based on historic trials and the most recent prospective studies, the 45 mg/m^2 of DNR should no longer be the standard-dose for induction therapy. Instead, for induction therapy of all age groups, DNR dose should be between 60 mg/m^2 to 90 mg/m^2 for 3 days, but the exact optimal dosage remains to be established[12].

2.2 New formulations of old agents

Liposomal encapsulation of drugs can reduce the toxicity and decrease drug doses with controlled-release effect. CPX-351 is a liposomal formulation that encapsulates cytarabine and daunorubicin at a 5:1 molar ratio. A recently completed phase 1 study[13] recommended that 90-minute infusions of 101 u/m^2 be given on days 1, 3, and 5 (1 u = 1 mg Ara-C + 0.44 mg DNR). The results showed that liposomal encapsulation of this chemotherapy changed the safety profile by reducing non-hematologic toxicities including hair loss, gastrointestinal toxicities and hepatic toxicity, while retaining hematopoietic cytotoxicity.

2.3 Targeted therapy regimens

In recent years, encouraging results have been achieved by using monoclonal antibodies for targeted therapy of the solid and hematologic malignancies. CD33 antigen is expressed in more than 90% of AML cells, while expression in normal tissue is very weak. Gemtuzumab ozogamycin (GO) is chemoimmunotherapy agent consisting of a monoclonal antibody against CD33 conjugated to calichemycin. GO triggers apoptosis when hydrolyzed in the leukemic blasts. GO has been approved by the U.S. FDA for the treatment of the elderly (> 60 years) with AML in first relapse. Standard induction regimen with or with out GO were compared in a randomized study which enrolled 1115 younger adults with AML. The preliminary analysis showed a similar CR rate in both arms, but a significantly improved DFS among patients receiving GO--51% versus 40% at 3 years (P = .008)[14]. However, due to toxicity concern and the lack of definite survival benefit after longer follow-up, FDA has recently withdrawn its approval.

A phase II study of My-FLAI aiming to assess toxicity and efficacy was done in patients with newly diagnosed AML aged more than 60 years[15]. The results showed that the four drug regimen My-FLAI was well tolerated in an elderly AML population, but its efficacy did not appear to be superior to that of standard "3+7" regimen[15].

2.4 New agents nucleoside analogues

Nucleoside analogues transform into active metabolites (triphosphate nucleoside analogues) in the cells and inhibit DNA synthesis. Clofarabine is a new nucleoside analogue, a potent inhibitor of both ribonucleotide reductase and DNA polymerase. At the 2009 ASH meeting, a few studies on Clofarabine were reported[16-18], either clofarabine alone or in combination with low-dose Ara-C, or high-dose Ara-C with the monoclonal antibody GO in the treatment of elderly AML or relapsed AML. Two novel nucleoside analogues, sapacitabine and elacytarabine, were also reported for the therapy of the elderly with refractory or relapsed AML[19,20].

2.5 FLT3 inhibitors (Fms-like tyrosine kinase 3 inhibitors)

The Flt3-internal tandem duplication (ITD) can be found in approximately 30% of all AML patients and confers a poor risk status characterized by an increased relapse rate and poor overall survival[21,22]. Moreover, Flt3-ITD-positive AML patients relapsing after allogeneic stem cell transplantation (SCT) have very limited therapeutic options. Sorafenib is a multikinase inhibitor that is approved for the treatment of metastatic renal cell and hepatocellular carcinoma. Sorafenib monotherapy has significant clinical activity in Flt3-ITD positive relapsed and refractory AML[23,24].

In addition, combination therapy with sorafenib was shown to be effective in reducing mutant clones in patients with FLT3 mutations but was not able to completely eradicate them[25]. These data suggest that sorafenib can achieve temporary disease control, but should be integrated into induction and consolidation regimens to achieve maximal outcome

2.6 Farnesyl-Transferase Inhibitor (FTI)

In recent years, studies have shown that Ras gene mutation plays an important role in leukemogenesis[26]. By inhibiting farnesyl protein transferase, FTI prohibits the Ras protein farnesylation, schizolysis and carboxyl methylation, thus disrupting the critical Ras

signaling pathway. Tipifarnib (± bortezomib) may represent an important option in a subset of high risk/frail AML patients[27].

2.7 Histone deacetylase inhibitors

Vorinostat is a new anti-cancer agent inhibiting histone deacetylase and has been shown to have some efficacy in treatment of AML[28]. Vorinostat in combination with idarubicin and ara-C has synergistic antileukemia activity in a sequence dependent fashion. Therefore, the combination of vorinostat, idarubicin and cytarabine is safe and active in AML. CR or CRi was achieved by 18% pts with MDS, 8% with relapsed/refractory AML, and 36% with untreated AML[29]. The combination of vorinostat with decitabine either concurrently or sequentially is possible without significant toxicity and shows activity in MDS and untreated AML[30].

2.8 DNA Methyl-transferase inhibitors

The demethylating agents 5-azacytidine and Decitabine are remarkably active, even at low doses with mild hematologic toxicity, in patients with high-risk MDS. This disease shares many poor prognostic features with AML of the elderly.

Decitabine: Decitabine inhibits DNA methyltransferase, leading to DNA hypomethylation and cell differentiation or apoptosis. A combination of decitabine and GO was found to be effective with low side effects in previously untreated or refractory/relapsed AML patients, especially in elderly patients[31]. The toxicities were minimal and the regimen can be safely delivered to older patients. The pioneering study by Pinto and coworkers[32] described 12 patients with AML who received Decitabine (90-120 mg/m^2 as a 4-h infusion 3 times daily for 3 days, repeated every 4–6 weeks). Three patients achieved a complete remission (CR) and one a partial remission (PR) ; extra-hematological toxicity was generally mild. Preliminary results of a trial using low-dose decitabine in older patients with AML were reported more recently[33]: Cashen and coworkers gave the drug over 1 h on 5 consecutive days (20 mg/m^2 per day), repeated every 28 days. Fifty-five patients with a median age of 74 years old were enrolled and treated with a median of three cycles : overall response rate was 25% (complete response rate, 24%) and median survival was 7.7 months.

5-Azacytidine: despite the fact that more than 100 trials of high dose 5-azacytidine were performed in AML in the 1970s and 1980s (mostly in combination with other chemotherapies), a very limited number of trials using this drug in AML have been published. When the CALGB compared the use of 5-Azacytidine to best supportive care in people with all risk groups of MDS, there was a trend toward a survival benefit in those patients who received the 5-Azacytidine[34]. There was a decrease in the P15 methylation associated with response. 5-azacytidine was approved by the FDA in 2004 for the treatment of MDS (all subtypes). Phase II studies of 5-azacytidine in MDS had been initiated by Silverman and the CALGB[35] (7 daily administrations of 75 mg/m^2, total dose 525 mg/m^2, repeated every four weeks); overall response rate of 49% was obtained, with 12% CRs and median response duration of 14.7 months. A pivotal phase III study of the CALGB[34] compared subcutaneous 5-azacytidine randomized against best supportive care (BSC), with the possibility of "cross-over" from BSC in case of progressive disease. An overall response rate of 60%, with 7% CRs and 16% PRs and median response duration of 15 months was achieved in the experimental arm. Quality of life was also significantly improved in 5-

azacytidine treated patients. Side effects included mainly myelosuppression and associated effects, particularly during the first cycles. Non-hematological toxicties, e.g. nausea and vomiting, were rare, but skin reactions occurred more frequently. The French ATU program[36] performed a retrospective analysis of 184 patients with refractory or relapsed AML who received azacytidine. 11% of the patients responded (7%CR, 3%CRi, 1% PR). It appears that single agent azacytidine has only limited activity in AML patients relapsed or refractory to intensive frontline therapy. Combination of azacitidine with bortezomib or low-dose GO was also studied in relapsed or refractory AML patients[37,38]. In a large confirmatory trial[39], 5-azacytidine was compared to conventional treatment as determined prior to randomization by the treating physician (either BSC, low-dose ara-C, or induction chemotherapy). Of 358 patients included, 179 were randomized to 5-azacytidine, 179 to conventional care (105 to BSC, 49 to low-dose ara-C, 25 to standard induction chemotherapy). Study drug was administered for a median of 9 cycles. 28.5% of patients in the experimental arm achieved CR or PR. Median survival was 24.4 months in the 5-azacytidine group compared to 15 months in the conventional care group (P=0.0001), with a doubling of the 2-year survival (50.8 vs. 26%, P<0.0001).

3. Valproic acid, an inhibitor of Histone Deacetylases (HDACs)

Valproic acid (VPA) is an inhibitor of class I HDACs. Over the last 5 years, the drug has been studied as either a single agent or in combination with various drugs including ATRA. VPA has provided a 50% overall response rate in low-risk MDS and a lower rate of response in high-risk MDS[40] and AML[41,42]. The contribution of ATRA probably was modest. Thus, the role of single-agent VPA may be rather limited in AML. Nevertheless, the drug in combination with an active drug such as decitabine, may have enhanced activity, as demonstrated in vitro[43]. A large phase II study of AML and MDS performed at the MD Anderson Cancer Center demonstrated the feasibility of DAC combined with 10 days of intravenous VPA[44].

3.1 Other agents in early clinical development

Voreloxin: is a first-in-class anticancer quinolone derivative that intercalates DNA, inhibits topoisomerase II, and induces apoptosis. A preliminary report on a voreloxin trial revealed clinical activity in previously untreated elderly (age ≥ 60) AML patients who are unlikely to benefit from standard chemotherapy[45]

Amonafide L-malate (AS1413): is a unique DNA intercalator, in combination with cytarabine produced a high complete remission rate and durable responses in both older and younger patients with secondary AML[46].

Ezatiostat hydrochloride: is a glutathione S-transferase P1-1 inhibitor, evaluated in myelodysplastic syndrome. In a phase I/II study[47], trilineage responses were observed in 4 of 16 patients (25%) with trilineage cytopenia. These responses were accompanied by improvement in clinical symptoms and reductions in transfusion requirements.

Lenalidomide: (LEN) is one of the three new drugs approved by the U.S. FDA to treat 5q-low-risk MDS. Lenalidomide has demonstrated multiple mechanisms of action[48]. In a recent phase II study[49] of LEN in combination with Ara-C and daunorubicin in high risk MDS/AML with del 5q, 28% responded. The results show that LEN combined with chemotherapy in AML treatment is feasible, without significant additional toxicity.

Ribavirin: The eukaryotic translation factor, eIF4E, is over expressed in AML, and is associated with poor prognosis. Ribavirin is clinically used as an antiviral molecule, and its structure is similar to the m(7)G cap of mRNA, thus inhibiting eIF4E-induced export and translation of sensitive transcripts[50].
ARRY-520: The kinesin spindle protein (KSP) plays a major role for the assembly of a normal bipolar spindle and is also required for cell cycle progression through mitosis. ARRY-520 is a potent, selective inhibitor of KSP[51].
AZD1152: Aurora B kinase plays a major role in regulating mitosis and is over expressed in AML. Also it's a highly potent and selective inhibitor of aurora B kinase. It has been shown to inhibit tumor growth in vivo[52].
AZD6244: is one of the orally bioavailable small molecule inhibitors of MEK kinase[53-55].
Terameprocol: The inhibitor of apoptosis protein (IAP), survivin, is a key regulator of cell cycles. In leukemic cells, survivin is involved in leukemia cell survival and resistance to chemotherapeutics and Flt-3 inhibitors[56].

3.2 Allogeneic Stem Cell Transplant (allo-SCT)

In patients with AML, published guidelines and treatment recommendations are usually the basis for starting the work-up process for allo-SCT[57]. However, only consistent recommendations would allow a standardized clinical practice. A comprehensive systematic literature search could allow to evaluate the best available evidence from controlled clinical trials. The following aspects were selected for systematic comparison: factors for risk assessment and categorization, role of type of donor, significance of allo-SCT in first or second complete remission and in relapse/progressive disease; and role of reduced intensity conditioning (RIC) regimens. The use of myeloablative and non-myeloablative allogeneic stem cell transplant represents a potentially curative approach for patients suffering from acute and chronic leukemias such as AML. Thousands of patients have been treated worldwide by the transplant of hematopoietic stem cells from a related or unrelated donor (available at: http://www.bmdw.org). However, it is obvious that not all patients diagnosed with AML will benefit from allogeneic stem cell transplant. Therefore, the establishment of definitive, clear, evidence-based recommendations as to which patients are likely to benefit from transplant is needed. Several interesting findings emerge when comparing recommendations for transplant in key guidelines: (i) for patients with relapsed or refractory disease, donor availability should be explored and patients should receive transplant, though this is not based on reliable evidence from genetically randomized studies; (ii) patients in CR1 with intermediate-or high-risk disease and an available matched related donor should receive allogeneic stem cell transplant (intermediate-risk: allo-SCT, reasonable option); (iii) for patients who lack a family donor the recommendations are not consistent; (iv) allogeneic transplant with reduced conditioning in patients with AML is feasible, but the superiority over standard therapeutic regimens is not yet proven. At this point in time, there is no doubt that hematopoietic allogeneic stem cell transplant is an effective clinical procedure with a curative ability, but intensive induction and consolidation chemotherapy may also be sufficient for many patients. But it is likely that only well-defined subgroups of patients with AML will benefit from stem cell transplant. The delineation of these specific patient groups will be a major objective of future clinical trials.
Transplant of patients with AML in first CR: in patients who achieved CR, the role of allo-SCT is still under discussion. A variety of clinical studies have tried to evaluate the benefit

of transplant in this situation, but most studies were non-randomized, non-controlled trials[3,5,6]. Only a few trials that were analyzed based on donor availability ('genetic' or 'biological' assignment) were useful as supporting evidence in the guideline recommendations, which were mainly based on cytogenetic risk factors. These methods of patient assignment often introduce biases. Therefore, some guidelines regard these trials as level II (cohort study) and not as level I evidence (randomized clinical trials). Cassileth et al.[58] reported a study of patients with AML aged 16–55 years with complete remission after induction therapy who were offered allogeneic transplant if a genotypically or phenotypically human leukocyte antigen (HLA)-matched or single-antigen mismatched family donor was available (n=113). Remaining patients were randomized to autologous transplant (n=116) or a single course of high-dose cytarabine (n=117). The distribution of karyotypes did not differ significantly among treatment groups. After a median follow-up time of 4 years, the authors found no evidence for significant differences in disease-free survival (DFS) between the chemotherapy group (35%), autologous transplant group (35%), and allogeneic transplant group (43%). Overall survival (OS) was marginally better after chemotherapy than following autologous or allogeneic transplant (52% vs. 43% vs. 46%). Twenty five percent of patients died after allogeneic transplant as compared to 14% following autologous transplant and 3% after chemotherapy. The subset analysis based on cytogenetic risk groups showed many methodological limitations of the study: a high proportion of patients did not receive the assigned therapy, which tends to reduce the measurable treatment effect in an intention-to-treat analysis.

The EORTC–GIMEMA (European Organization for Research and Treatment of Cancer–Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto) AML 8A trial[59] showed no significant difference in overall survival after a median follow-up of 6 years among patients receiving allogeneic transplant from a sibling donor (overall survival: 48%) versus patients without a donor (40%, p=0.24; patients received autologous transplant or conventional chemotherapy).

A higher incidence of early mortality after allogeneic transplant was counterbalanced by a lower incidence of late mortality. In the EORTC AML 10 trial[60] these results were confirmed, with the exception of the high-risk group. In total, the survival rate at 4 years was 58.3% in the allogeneic, sibling donor group versus 50.8% in the autologous transplant group (p=0.18). In the high-risk group, in patients receiving allogeneic transplant the overall survival at 4 years (50.2%) was significantly better than after chemotherapy or autologous transplant (29.4%). In the standard-risk group and the low-risk group the results for overall survival were similar.

However, the GOELAM (Groupe Ouest Est Leucemies Aigues Myeloblastiques) trial[61] reported no survival benefit for patients receiving an allogeneic transplant regardless of cytogenetic risk group. Interestingly, a trend toward better survival at 4 years following allogeneic transplant was more pronounced in the low-risk group (71.4% vs. 66.5%; p=0.6) and the high-risk group (41% vs. 30%, p=0.97) compared to the intermediate-risk group (40.5% vs.56.5%, p=0.08). The BGMT 87 trial[62] reported overall survival only for the entire patient population and not stratified for risk groups. In patients receiving allogeneic transplant, 3-year survival was 65% in the donor group (n=36) and 50.9% in the no-donor group (n=60) receiving chemotherapy or autologous transplant. An analysis from all trials undertaken by the BGMT shows an improved survival only for the Intermediate and high-risk population[62]. The MRC AML 10 trial by Burnett et al.[63] evaluated 1063 patients on a

donor versus no-donor basis. All patients received four courses of induction chemotherapy followed by consolidation chemotherapy, after which patients with an HLA-matched sibling donor and in appropriate condition were scheduled to receive an allogeneic transplant. The remainder was randomized between autologous transplant and no further therapy. Sixty-one percent of patients with a donor underwent transplant in first remission. In a donor versus no-donor analysis, significant benefit in disease-free survival and overall survival was seen only in the standard-risk cytogenetic group (DFS: 50% vs. 39%, p=0.001; OS: 55% vs. 44%, p=0.01). There were twice as many deaths in first remission among patients with a donor than among patients with no donor (19% vs. 9%; p<0.001).

Recently, the results of three trials from the Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research (HOVON/SAKK) based on a donor versus no-donor analysis in patients with AML in first remission were published as an individual patient data (IPD) analysis[64]. Based on the available IPD, the study included a total of 1032 patients from the trials. An HLA-identical sibling donor was available for 32% of patients, whereas 58% of patients lacked such a donor. Following risk-group analysis, disease free survival was significantly better for patients with available donor and standard- or high-risk profile (p=0.01 and p=0.003) and also better for patients younger than 40 years (p<0.001). However, the improved disease-free survival in the donor group did not translate into significantly better overall survival (p=0.07). Treatment-related mortality was significantly higher in the donor group (21% vs. 4%; p<0.001).

Three meta-analyses investigated the apparent heterogeneity of clinical study results. Cornelissen et al. [64] performed a meta-analysis based on published data including more than 4000 patients with AML in first remission enrolled in the HOVON/SAKK studies, the Medical Research Council (MRC) studies, the trials of the EORTC, and the BGMT studies. Disease-free survival and overall survival were analyzed, stratified for cytogenetic risk profile and age. Overall, transplant from a family donor statistically significantly prolonged disease-free survival in patients with intermediate- and high-risk profiles, but not in patients with a low-risk profile. This effect was pronounced but not restricted to patients below the age of 35 years. However, a benefit for overall survival in patients receiving stem cell transplant from a related donor was seen only in patients with intermediate- and low-risk disease up to the age of 35 years. In this analysis there was no evidence for improved outcomes in the favorable-risk group. These results are in accordance with the meta-analysis published by Koreth et al.[6] in 3638 patients with AML in first CR. However, Yanada et al.[65] identified a beneficial effect of allogeneic transplant in these patients limited to the high-risk group.

In summary, there is only a limited number of phase III trials evaluating the role of allo-SCT in patients with AML in first remission. The results of these trials are heterogeneous, and often limited to matched-related donor transplant.

Transplant in relapse/progressive disease: it is generally accepted that the overall prognosis of patients with relapsed or progressive disease is poor. Especially in patients with initial duration of remission below 1 year, the success with standard regimens for inducing second remission is rare. Therefore, it is not surprising that in this situation most treatment guidelines recommend allogeneic transplant once a patient has achieved second remission. However, we did not identify any randomized trial in literature search addressing this clinical situation. In a phase II study, Schmid et al.[66] treated 103 patients with refractory AML using dose-reduced chemotherapy followed by allogeneic transplant

from a related or unrelated donor. Refractory disease was defined as primary induction failure, relapse within 6 months after induction, or second relapse. Overall, 1 year after transplant the authors reported a disease free survival of 47% and an overall survival of 54%. After a follow-up of 4 years, disease-free survival and overall survival declined to 30% and 32%. The risk for treatment failure was significantly increased in patients who received more than two cycles of chemotherapy before stem cell transplant, in patients with primary induction failure, bone marrow infiltration of more than 50% blasts, and more than a median of 215 days from diagnosis to transplant, or in patients with low CD34 cell count in the graft and if stem cells from a related donor were used. While the risk for non-relapse mortality increased when using an unrelated donor, age, sex, and underlying karyotype were not predictive for outcome. Minimal residual disease (MRD), mostly defined as the positive detection of genetic AML-specific mutations during microscopically diagnosed complete remission, is often examined in the follow-up period after induction therapy for leukemia. In small cohort of 45 patients, Laane et al.[67] claimed a benefit by allogeneic transplant for those patients who were identified with detectable MRD after standard therapy.

Reduced intensity conditioning: reduced intensity conditioning has broadened the use of allogeneic stem cell transplant to elderly patients and patients with comorbidities. Allogeneic transplant is no longer restricted to younger, fitter patients who are better able to tolerate the toxicities of a myeloablative regimen. The use of a less intensive approach potentially results in a reduced leukemia cell kill, which in turn increases the risk for relapse and a higher incidence of engraftment failure. Uncertainty remains regarding the frequency of graft-versus-host disease (GvHD) after reduced intensity allografts. Usually, a higher dose of immunosuppressive agents or the use of long-acting agents is recommended to reduce the rate of GvHD after transplant, thereby increasing the risk of relapse. In conclusion, there is an urgent need to define the role of allogeneic transplant in the mixed chimérisme setting. Unfortunately, published literature is often based on single centre experience with small numbers of patients. The Seattle experience is derived from large multicenter studies including a high number of patients. These studies have refined the optimal non-myeloablative treatment procedure, but they do not compare reduced intensity allografts with other treatment strategies[68].

At our knowledge, two randomized controlled studies, evaluating the role of reduced conditioning followed by allogeneic stem cell transplant for AML, have been published. Mothy et al.[69] assigned 95 newly diagnosed adult patients with AML in first complete remission on a donor versus no-donor basis. All patients had a high-risk karyotype or clinical profile. Based on 'biological' randomization, patients with a matched sibling donor (n=35) were assigned to a transplant arm using reduced conditioning, whereas patients lacking such a donor (n=60) were assigned to standard treatment procedures. In an intention-to-treat analysis, 4-year disease-free survival was significantly higher in the donor group (54%) as compared to the no-donor group (30%; p=0.01). Furthermore, overall survival was significantly higher in the donor group as compared to the no-donor group (p=0.04). Transplant-related mortality was 12%.

Estey and colleagues[70] prospectively assessed the applicability of reduced intensity conditioning in patients with AML or MDS. Of 99 patients who entered complete remission after induction chemotherapy, 14 received an allogeneic transplant (13 siblings). The authors conducted a matched-pair analysis, comparing patients receiving chemotherapy with

patients who underwent transplant. Matching criteria were age, cytogenetics, and time between achieving CR and transplant. There was a significantly longer disease free survival in the transplanted patients, but the results for overall survival were similar between patients receiving transplant and patients receiving chemotherapy.
In a large retrospective trial performed by the EBMT[71], 315 patients with AML or MDS who received reduced intensity conditioning were compared with 407 patients who received a Myeloablative approach. In multivariate analysis, acute GvHD and transplant-related mortality were significantly decreased, and relapse incidence was significantly higher after reduced intensity conditioning.

3.3 Autologous Stem Cell Transplantation (auto-SCT)

For patients with AML who are unable to secure an acceptable HLA donor, the role of autologous stem cell transplantation (auto-SCT) has remained controversial. Its effectiveness remains unclear as, when analyzed on intention-to-treat strategies, a significant number do not undergo the procedure, whereas others seem to fail therapy from pre transplant recurrences. Recently, Novitzky et al.[72] compared the outcome of patients in first remission of AML who actually underwent autologous or allogeneic transplantation. The choice for the type of graft was based on availability of HLA identical siblings. Patients received myeloablative conditioning followed by allogeneic or autologous cytokine mobilized peripheral blood stem cell transplantation. For prophylaxis of graft-versus-host disease (GVHD), grafts were incubated ex vivo with anti-CD52 antibodies and patients were prescribed cyclosporin until day 90. Patients were stratified by clinical and laboratory factors as well as cytogenetic risk. The endpoints were treatment-related mortality (TRM), disease-free survival (DFS), and overall survival (OS). The median presentation age for both transplant groups was 35 (14-60) years. Of the 112 consecutive patients achieving remission, autologous or allogeneic grafts were transplanted to 43 and 32 patients, respectively. There was no significant difference in the presentation clinical features, laboratory parameters, marrow morphology, or proportion of low and intermediate cytogenetic risk for both transplant options. Treatment mortality as well as relapse rate was similar (14% and 15%; 39% and 27%, respectively). At a median of 1609 and 1819 post transplant days, 56% and 63% in each group survived. In univariate analysis performance status, cytogenetic risk, morphologic features of dysplasia, blast count, and lactate dehydrogenase (LDH) were significant factors for survival. Although for the entire group there was no difference in survival between both modalities, all patients with unfavorable cytogenetics receiving an autologous graft died of disease recurrence (3-year survival 35% versus 0%; P = 0.05). They conclude that patients with AML who have low or intermediate cytogenetic risk undergoing myeloablative conditioning followed by autologous or allogeneic T cell-depleted stem cell transplantation appeared to have similar outcome. However, those with unfavorable karyotype are unlikely to be cured with autologous grafts and are candidates for experimental modalities.

3.4 Other regimens for refractory /relapsed AML

High-dose cytarabine (HiDAC) is commonly used for re-induction of relapsed or refractory AML. Recently, Thomas et al.[73] et al reported a novel, timed-sequential regimen that takes advantage of synergy when mitoxantrone is given after cytarabine. Those patients received HiDAC/mitoxantrone regimen, with cytarabine at 3 g/m^2 over four hours on days 1 and 5

plus mitoxantrone at 30 mg/m^2 over one hour immediately following the HiDAC on days 1 and 5. HiDAC/mitoxantrone induction was well tolerated and complete remission was achieved in 89%. of patients.

To further enhance the CR rate in refractory/relapsed AML, the Japanese Adult Leukemia Study Group (JALSG) reported a phase II study of FLAGM (Fludarabine + High-Dose Ara-C + G-CSF + mitoxantrone) in 41 patients with relapsed or refractory AML[74]. FLAGM yielded a 70% response rate in either relapsed or refractory AML patients. Although randomized studies are still needed, FLAGM appears to be a good option for the treatment of either relapsed or refractory AML patients.

4. Conclusions: Future directions

Achieving a cure for AML, even for younger adult patients with de novo AML, remains a challenge. While more than 70% of such patients will enter a first CR1 after induction chemotherapy, a substantial number experience disease relapse. Allo-SCT is a curative treatment option for younger patients with AML in CR1. However, concerns regarding allo-SCT–related toxicity, and questions regarding its benefit, limit its use for patients who have attained an initial remission. Alternative therapies include intensive consolidation chemotherapy or auto-SCT. The current consensus, reflected in treatment guidelines of the National Comprehensive Cancer Network (V1.2009: available at http://www.nccn.org), is based on cytogenetic stratification into good-, intermediate-, and poor-risk AML. Compared with non-allo-SCT therapies, allo-SCT has significant relapse-free survival and overall survival benefit for intermediate- and poor-risk AML but not for good-risk AML in CR1.

Prognostic markers, such as NPM1, Flt3-ITD, and cytogenetic abnormalities have made it possible to prospectively formulate aggressive treatment plans for unfavorable AML. If no Flt3-ITD mutation is present, *CEBP*α and *NPM1* are generally associated with a favorable prognosis, and testing will be important in defining biologic subtypes that require less therapy. The presence of some of these mutations may modify the effect of others, so the establishment of a panel of significant markers may be needed to adequately assess risk and plan care. However, the long-term survival of AML with unfavorable factors remains unsatisfactory. Prolonged survival without curing high risk MDS/AML patients suggests that disease modification instead of cure of AML patients may be an alternative goal of treating elderly patients not suitable for aggressive therapy. New regimens and novel agents targeting specific pathways reviewed in this report may bring AML treatment into a new era.

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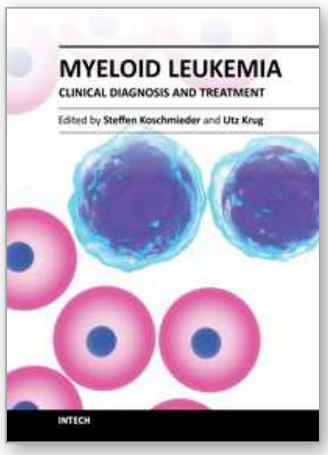

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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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