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Acute Promyelocytic Leukemia Lacking the Classic Translocation t(15;17)

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1. Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by the reciprocal translocation t(15;17)(q22;q12) resulting in the fusion gene *PML-RARA* and an oncoprotein that impairs myeloid differentiation (Arber et al., 2008; de The et al., 1990; Rowley et al., 1977). Morphological and clinical characteristics include hypergranular leukemic promyelocytes, Auer rods, and coagulopathy. The use of all-trans retinoic acid (ATRA) has revolutionized the management of this disease that has become the most curable form of AML in adults (Castaigne et al., 1990; Tallman et al., 1997). In relapsed APL, arsenic trioxide can induce complete morphological, cytogenetic and molecular remission (Douer and Tallman, 2005; Soignet et al., 1998).

Cases lacking the classic t(15;17) are divided into two separate groups that behave differently and are now considered different disease entities (Arber et al., 2008). The first group represents cryptic and complex APL where t(15;17) is absent on routine cytogenetic studies but *PML-RARA* is present on molecular studies (Grimwade et al., 2000). This group shares the same phenotype, prognosis, and sensitivity to ATRA as classic APL, and is thus managed similarly. The second group, "AML with a variant *RARA* translocation", is no longer considered part of APL and includes acute myeloid leukemias with translocations involving *RARA* and a variety of partner genes other than *PML* (Arber et al., 2008). Compared to classic APL, these leukemias often exhibit significant differences in malignant phenotype and sensitivity to ATRA which will be further explored in this chapter.

2. Clinical characteristics

APL represents less than 10% of all AML, but seems to be over-represented in Hispanics (Yamamoto and Goodman, 2008). The median age of presentation is approximately 40 years (Vickers et al., 2000). Leukocytosis is only seen in about 25% of patients, and organomegaly is rarely found on diagnosis. The most common presenting signs are pancytopenia, fever, anemia, and bleeding. The latter can be fatal especially if occurring in the central nervous system (CNS), and is due to the combination of thrombocytopenia and the dreaded coagulopathy of APL (Warrell et al., 1993).

3. Morphology

Abnormal promyelocytes are larger than their normal counterparts, with a nucleus that is often bilobed or kidney-shaped. 75% of APL cases are hypergranular (M3) with densely-packed cytoplasmic granules that are bright pink, red, or purple, in addition to Auer rods in bundles called "faggot cells". The remaining 25% of cases are microgranular or hypogranular (M3v), the granules being visualized by electron microscopy but not light microscopy, and the cytoplasm may contain a few fine azurophilic granules.
In APL, myeloperoxidase (MPO) is strongly positive in all leukemic promyelocytes, and this can be especially helpful in microgranular APL which is sometimes confused with acute monocytic leukemia (Arber et al., 2008).

4. Immunophenotype

APL cells are usually CD13 positive and especially CD33 positive, but are characterized by low or absent expression of HLA-DR, CD34, CD11a, CD11b, CD18, and CD117 (Paietta et al., 2004). Hypogranular APL frequently coexpresses CD34 and CD2 (Exner et al., 2000). Expression of CD56 has been observed in about 20% of cases and confers a worse outcome (Ferrara et al., 2000).

5. Pathogenesis

APL is caused by the reciprocal translocation t(15;17)(q22;q12) that results in the fusion gene *PML-RARA* and an oncoprotein that impairs myeloid differentiation (Grignani et al., 1993). *PML* and *RARA* are both involved in normal hematopoiesis, and disruption of their physiologic roles by the formation of *PML-RARA* is essential to leukemogenesis.
PML possesses physiologic growth suppressor and proapoptotic properties that are disrupted by *PML-RARA*, possibly by the abnormal positioning of *PML* away from the nuclear body structure, thus contributing to leukemic transformation (Wang et al., 1998). Following this logic, treatment with ATRA restores the normal localization of *PML*, allowing the resumption of its physiologic functions.
On the other hand, *RARA* normally binds to response elements at the promoter region of target genes through heterodimerization with the retinoid X receptor (*RXR*). *RARA-RXR* results in the recruitment of nuclear corepressors (N-CoR) and histone deacetylase (HDAC) that repress transcription and inhibit differentiation (Grignani et al., 1993). This is thought to take place through epigenomic changes including histone deacetylation or methylation (Licht, 2009) and could have therapeutic implications in the future, especially as to the efficacy of histone deacetylase inhibitor in APL refractory to conventional treatment with ATRA. Physiologic amounts of retinoid acid (RA) unbind the N-CoR from *RAR-RXR*, allowing for activation of transcription of *RARA* target genes and myeloid differentiation. In the presence of *PML-RARA*, normal concentrations of RA are not enough for that separation and pharmacologic doses of ATRA are needed to allow myeloid differentiation (Warrell et al., 1993). Arsenic trioxide (ATO) can also lead to differentiation, but it does so by inducing degradation of the *PML-RARA* fusion transcript. Both drugs have recently been shown to also work on an entirely different level in APL by eradicating "leukemia-initiating cells" or "leukemic stem cells" (Nasr et al., 2009), leading to think that their combination in induction regimens could result in higher rates of prolonged remissions and cure.

6. Genetics

6.1 Classic t(15;17) APL

Around 92% of APL patients have the balanced t(15;17), leading to the fusion of the retinoic acid receptor-alpha (*RARA*) gene on chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15 (Grimwade et al., 2000) (Fig. 1). FISH uses a dual color dual fusion probe to detect *PML-RARA* rearrangements. The typical normal FISH pattern for the dual color, dual fusion probe is 2 red signals (2R) and 2 green signals (2G) for the *PML* and *RARA* loci respectively. When t(15;17) is present, the characteristic FISH pattern is one red, one green and two fusion signals (Fig. 2).

Whereas the breakpoints in *RARA* are invariably at intron 2, those in *PML* can occur at any one of three breakpoint cluster regions (Bcr): intron 6 (Bcr1), exon 6 (Bcr2), and intron 3 (Bcr3) (Pandolfi et al., 1992). The 3 respective ensuing mRNA types, long (L)-form, variable (V)-form, and short (S)-form, can exhibit different phenotypes but do not affect complete remission (CR) rate or disease-free survival (DFS). The S-form, for example, is associated with increased leukocytosis which by itself is an adverse risk factor in APL, but after adjusting for that, does not independently influence CR rate and OS (Gallagher et al., 1997). The V form, originally thought to be less sensitive to ATRA, was later shown to be as equally sensitive to it as the other two types (Slack et al., 2000).

6.2 Cryptic and complex APL

As mentioned before, t(15;17) is absent in around 8% of patients diagnosed with APL (Grimwade et al., 2000), which should lead to the adoption of *PML-RARA* as the hallmark of APL. Cases lacking t(15;17) are divided into two separate disease entities: on one hand, cryptic and complex APL that share the same phenotype, prognosis, and sensitivity to ATRA as classic APL; and on the other hand, AML with a variant *RARA* translocation (Arber et al., 2008) which will be discussed later in this chapter.

In cryptic and complex APL, the classic t(15;17) is absent on routine cytogenetic studies but *PML-RARA* is present on molecular studies; the leukemia is morphologically and clinically similar to t(15;17) positive APL and is treated as such. The European working party was crucial in characterizing the rare APL cases lacking the classic t(15;17) on routine cytogenetic studies. 4% of the cases represented cryptic/masked APL with submicroscopic insertion of *RARA* into *PML* leading to the expression of the *PML-RARA* transcript, while 2% had complex variant translocations involving chromosomes 15, 17 and an additional chromosome, and were sub-classified as: (a) complex variant t(15;17) due to a 3-way balanced translocation involving 15q22, 17q21, and another chromosome; (b) simple variant t(15;17) involving 15q22 or 17q21 with another chromosome; and (c) very complex cases (Grimwade et al., 2000).

In these unusual cases, the diagnosis can be missed by conventional cytogenetic studies, and molecular methods are needed such as fluorescence in situ hybridization (FISH) (Fig. 2), reverse transcriptase polymerase chain reaction (RT-PCR) and direct sequencing. FISH is often not sensitive enough to detect small cryptic insertions (Han et al., 2007; Kim et al., 2008; Wang et al., 2009), while RT-PCR can also face technical challenges such as atypical *PML-RARA* rearrangement with new breakpoints in the *PML* gene that cannot be amplified with conventional primers (Barragan et al., 2002; Park et al., 2009), insertions of the *PML* gene to the *RARA* but too far apart to permit elongation and amplification of the *PML-RARA* sequence (Tchinda et al., 2004), or submicroscopic deletions of the 3' *RARA* (Han et al., 2009).

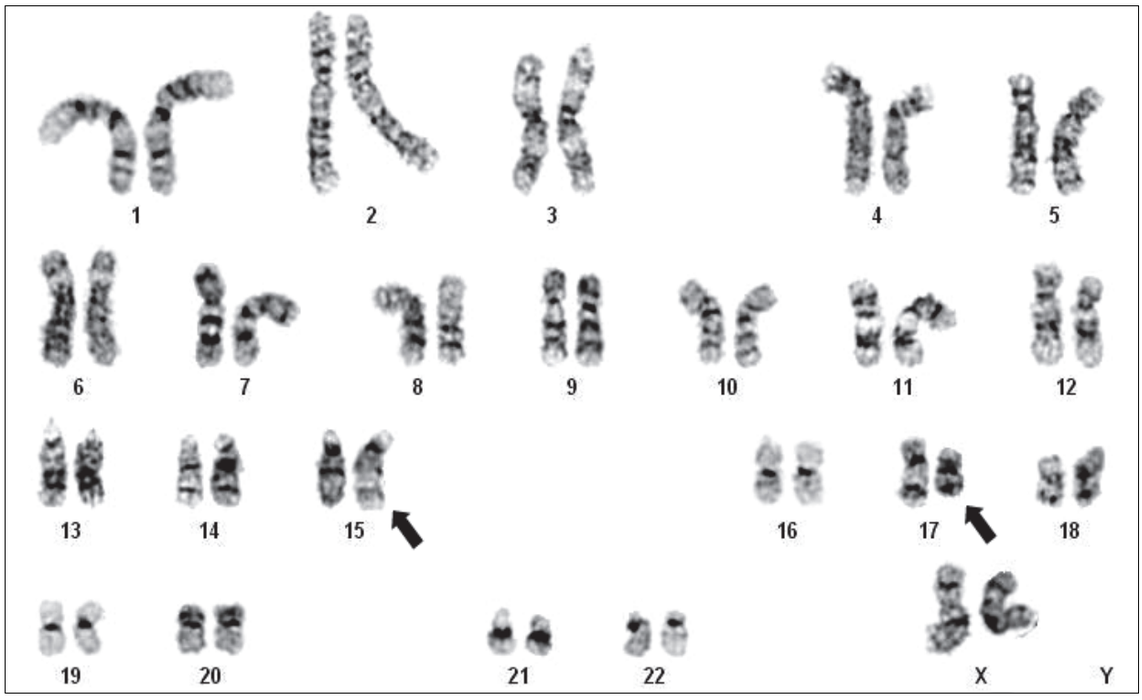

Fig. 1. G-banded karyotype with t(15;17)(q22;q21) at arrows.

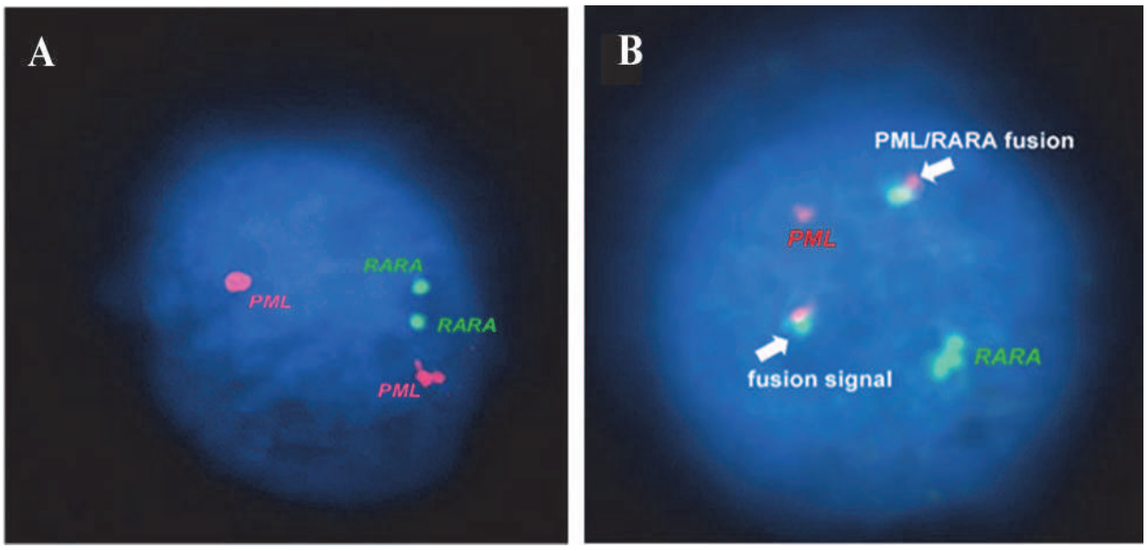

Fig. 2. Dual color dual fusion break apart probe for detection of *PML-RARA* rearrangement. Panel A shows a normal FISH pattern (2R,2G), whereas panel B reveals fusion of the *PML* and *RARA* loci at arrows.

6.3 AML with a variant *RARA* translocation

This term is now used by the WHO (World Health Organization) to designate a subset of acute myeloid leukemias morphologically similar to APL, but lacking both t(15;17) by cytogenetics and *PML-RARA* by FISH and RT-PCR (Arber et al., 2008). They do, however,

show different variant translocations involving *RARA* and 1 of 7 partner genes: *ZBTB16* (previously known as promyelocytic leukemia zinc finger gene or *PLZF*) on chromosome 11q23 (Licht et al., 1995), *NUMA1* (nuclear matrix-mitotic apparatus protein 1 gene) on chromosome 11q13 (Wells et al., 1996), *NPM1* (nucleophosmin gene) on chromosome 5q35 (Corey et al., 1994; Hummel et al., 1999), *STAT5B* (signal transducer and activator of transcription 5 beta) on chromosome 17q21.1-21.2 (Zelent et al., 2001), *PRKAR1A* (protein kinase, cAMP-dependent, regulatory, type I, alpha) on chromosome 17q24 (Catalano et al., 2007), *FIP1L1* (factor interacting with PAP 1-like 1) on chromosome 4q12 (Buijs and Bruin, 2007), and *BCOR* (BCL6 corepressor gene) on chromosome X (Yamamoto et al., 2010). Of the partner genes, the first 4 were included in the latest WHO classification, while the last 3 have been described since. As with other hematological malignancies, partner genes affect both neoplastic phenotype and response to treatment including ATRA, making their identification crucial in the evaluation of these patients.

6.3.1 ZBTB16-RARA

The *ZBTB16* or *PLZF* gene encodes for a zinc finger transcription factor of 673 amino acids (Chen et al., 1993). Its expression may play a role in the life of hematopoietic stem cells and seems to be down-regulated with differentiation (Shaknovich et al., 1998). Like *PML*, it possesses tumor suppressor activity that seems to be disturbed by t(11;17)(q23;q21) (Zelent et al., 2001). The European working party on APL found the t(11;17)(q23;q21) translocation in 0.8% of APL patients (Grimwade et al., 2000). The first case was identified in a Chinese patient from Shanghai (Chen et al., 1993), and more than 16 cases have been described since. The clinical presentation is usually indistinguishable from APL, with a low peripheral WBC count and a preponderance of promyelocytes in the bone marrow. The leukemic cells are usually microgranular, have a regular nucleus instead of bilobed, no Faggot cells, and there is often an increased number of Pelger-Huet-like cells (Sainty et al., 2000). The blasts are typically HLA-DR and CD34 negative, CD13 and CD33 positive. Several cases were strongly positive for the CD56 NK cell antigen.

The tumor suppressor properties of *ZBTB16* are thought to be inhibited by the *ZBTB16-RARA* fusion protein in t(11;17)(q23;q21). Except for anecdotal reports, patients with *ZBTB16-RARA* are resistant to ATRA since pharmacological doses of the drug fail to dissociate *ZBTB16* from the co-repressors (Licht et al., 1995).

6.3.2 NUMA1-RARA

The nuclear matrix-mitotic apparatus protein 1 gene (*NUMA1*) on chromosome 11q13 is a 236 kDa protein that serves in the completion of mitosis, is thought to be involved in the regulation of transcription and is affected by post-translational changes (Harborth et al., 2000; Saredi et al., 1996). So far, there's only been a single report of a patient with *NUMA1-RARA,* a 6 month-old boy who was diagnosed with APL with atypical features, received ATRA and was in complete remission (CR) more than 24 months following a bone marrow transplant (Wells et al., 1997; Wells et al., 1996). The pathogenesis of this leukemia is not well understood, but is thought to share several features with *PML-RARA* APL.

6.3.3 NPM1-RARA

The nucleophosmin gene *(NPM1)* plays a role in several important cell functions from the transportation of ribosomal precursors between cytoplasm and nucleolus (Szebeni et al.,

1997), to cell growth control (Zelent et al., 2001) and activation of transcription (Shi et al., 1997). It had been implicated in hematological malignancies including anaplastic lymphoma (Morris et al., 1994) and myelodysplastic syndrome (Yoneda-Kato et al., 1996). The *NPM1-RARA* fusion is a rare variant translocation (less than 0.5%) and has so far been reported in pediatric patients, with absent Auer rods but otherwise variable morphology. In contrast to classic APL, CD13 is negative, but the rest of the immunophenotype is similar to classic APL including absence of CD56. The reported cases have been very sensitive to treatment with ATRA (Corey et al., 1994; Grimwade et al., 2000; Hummel et al., 1999; Redner et al., 1996).

6.3.4 STAT5B-RARA

STAT5B is one of many latent cytosolic transcription factors to be activated by janus kinase (JAK) tyrosine kinases, allowing it to move to the nucleus where it regulates gene transcription (Arnould et al., 1999). To date, only 4 cases of AML with *STAT5B-RARA* have been reported, all men in their fourth to sixth decade of life, with a predilection for disseminated intravascular coagulation (DIC) but otherwise heterogeneous clinical, morphologic and immunophenotypic characteristics. Finally, S*TAT5B-RARA* is resistant to ATRA, similarly to *ZBTB16-RARA.* (Arnould et al., 1999; Iwanaga et al., 2009; Kusakabe et al., 2008).

6.3.5 PRKAR1A-RARA

PRKAR1A refers to protein kinase, cAMP-dependent, regulatory, type I, alpha.

Protein kinase A (PKA) is a multimeric protein which activity is dependent on cyclic adenosine monophosphate (cAMP). Downregulation of PKA occurs when phosphodiesterase, one of the substrates activated by the kinase, converts cAMP to AMP, effectively decreasing cAMP that can activate PKA. There's only one reported case of AML with *PRKAR1A-RARA* in a 66 year-old man. He presented with a normal WBC count, had a hypercellular marrow with 88% hypergranular promyelocytes, regular nuclei, and absent Auer rods and faggot cells. MPO was strongly positive, but expression of CD13, CD33, and CD11b was weak. The cells were negative for CD2, CD19, CD34, CD56, CD117, and HLA-DR (Catalano et al., 2007).

6.3.6 FIP1L1-RARA

Human FIP1 is an integral subunit of cleavage and polyadenylation specificity factor (CPSF), and plays a significant role in poly(A) site recognition and cooperative recruitment of poly(A) polymerase to the RNA (Kaufmann et al., 2004). Only 2 cases of *FIP1L1-RARA* have been described, and the entity seems to be sensitive to ATRA. The first case involved a 90 year-old woman who was clinically diagnosed with APL and achieved a complete remission by oral administration of ATRA alone. No further details were described in the paper as to clinical presentation, morphology, or immunophenotypic analysis (Kondo et al., 2008).

The second case involved a 20 month-old boy who was diagnosed with juvenile myelomonocytic leukemia after presenting with leukocytosis and anemia. Bone marrow aspirate showed hypercellularity including 11% promyelocytes, 25% myelocytes, 12% metamyelocytes, and 8% myelomonoblasts. These cells were hypergranular but had regular nuclei and no Auer rods. Immunophenotypic analysis was not published. Unfortunately, the patient did not receive ATRA, had an allogeneic stem cell transplant but died from relapse a few months later.

6.3.7 BCOR-RARA

As its name implies, *BCOR* is a corepressor of transcription through the oncoprotein BCL6, and its activity could be disrupted by the formation of *BCOR-RARA* (Huynh et al., 2000).
There's only one such case reported in the literature of a 45 year-old male patient who presented with leukocytosis and coagulopathy. Leukemic cells were MPO positive and less granular than classic APL. Interestingly, the cytoplasm contained periodic acid–Schiff rectangular and round cytoplasmic inclusion bodies and lacked Auer bodies and faggot cells. Immunophenotypic analysis showed HLA-DR negativity but positivity for CD33, CD13 and CD56. The patient was clinically responsive to ATRA but had several relapses with chemotherapy and ATRA (Yamamoto et al., 2010).

7. Treatment

In the previous section, we depicted the reported cases of AML with a variant *RARA* translocation, their response to treatment, and their varying sensitivity to ATRA depending on the partner gene. We will now discuss the management of classic APL, and cryptic and complex APL; these all share the same phenotype, prognosis, and sensitivity to ATRA, and therefore are treated similarly.

7.1 Induction therapy

When left untreated, APL is the deadliest form of AML with a median survival of less than 30 days (Hillestad, 1957). The introduction of ATRA in 1980 (Breitman et al., 1980) completely revolutionized the management of this disease that now boosts complete remission rates of 80 to 95% and cure rates of around 80% (Sanz and Lo-Coco, 2011). ATRA sets off the differentiation of malignant promyelocytes into mature granulocytes, improves homeostasis and shortens the duration of the dreaded coagulation syndrome of APL. It also generates the eradication of "leukemia-initiating cells" or "leukemic stem cells", a property shared by arsenic trioxide (ATO). In mice, a combination of both drugs can actually result in the elimination of leukemia-initiating cells and effectively "cure" APL (Nasr et al., 2009), opening the door to future trials combining ATRA and ATO without the use of chemotherapy. As mentioned before, if APL is suspected clinically and cytologically, ATRA should be promptly started even if cytogenetic and molecular confirmations of the diagnosis are pending.
Because of the short duration of CR with ATRA alone, and the known sensitivity of APL to anthracyclines (Head et al., 1995), the current standard induction regimen in APL is the administration of ATRA with anthracycline-based chemotherapy. This combined approach has been shown to be superior to a previously adopted sequential treatment of ATRA followed by chemotherapy (Fenaux et al., 1999). The median time to CR ranges from 38 to 44 days but could be as long as 90 days. In addition to its effect on CR, chemotherapy controls leukocytosis that is common when ATRA is used alone. In patients who have contraindications to anthracycline chemotherapy, the combination of ATRA and arsenic trioxide (ATO) for induction treatment should be considered (Sanz et al., 2009). The current standard chemotherapy regimens use daunorubicin with cytarabine or idarubicin alone, while there's a lack of experience and data with other anthracyclines. These 2 regimens have indirectly yielded comparable CR rates (Fenaux et al., 1999; Mandelli et al., 1997). When daunorubicin was used without cytarabine in one randomized prospective trial of young

patients with APL, the CR rates were similar but there were more relapses and lower overall survival in patients who did not get cytarabine (Ades et al., 2006). The additional benefit conferred by cytarabine, however, did not apply to all patients and was only observed in those with WBC > $10x10^9$/L (Ades et al., 2008) who are high-risk patients by Sanz's risk stratification (Table 1) (Sanz et al., 2000; Sanz et al., 2004). Based on these results and the findings of other trials suggesting a similar role for cytarabine in consolidation (Sanz and Lo-Coco, 2011), we recommend that APL patients younger than 60 years old with WBC > $10x10^9$/L receive cytarabine in addition to ATRA and an anthracycline. Other indicators of relapse, such as CD56 positivity, do not currently alter treatment decisions (Ferrara et al., 2000).

7.2 Consolidation therapy

Five to six weeks following induction, patients should be re-evaluated with bone marrow aspirate/biopsy and cytogenetics, while RTC-PCR for *PML-RARA* is not required since the transcript will still be detectable in about half of patients. Those in remission (> 90% of patients) will proceed with consolidation treatment to prevent relapse. This involves the use of an anthracycline (± cytarabine in high-risk patients), in addition to ATRA (Sanz et al., 2004; Sanz et al., 2008), but different regimens are still being prospectively studied.

7.3 Maintenance therapy

Molecular remission is required at the end of consolidation treatment, after which maintenance ATRA will increase disease-free survival and improve the 10-year cumulative incidence of relapse (Ades et al., 2010; Tallman et al., 2002). The most commonly used maintenance regimen lasts for 1 year and encompasses ATRA 45 mg/m2 orally daily for 15 days every 3 months or 7 days every 2 weeks, 6-mercaptopurine 60 mg/m2 orally every evening, and methotrexate 20 mg/m2 orally every 7 days (Avvisati G, 2003). Patients require close surveillance for toxicities, myelosuppression, and abnormal liver function tests, in addition to RTC-PCR every 3 months to monitor for disease relapse.

Risk stratification		**3-year DFS**
Low risk	**WBC ≤ $10x10^9$/L, PLT > $40x10^9$/L**	**97%**
Intermediate risk	**WBC ≤ $10x10^9$/L, PLT ≤ $40x10^9$/L**	**97%**
High risk	**WBC > $10x10^9$/L**	**77%**

Table 1. Risk stratification of APL patients based on WBC and Platelet (PLT) counts, and corresponding 3-year disease-free survival (DFS) following induction and consolidation therapies with ATRA + anthracycline-based chemotherapy, followed by standard maintenance (Sanz et al., 2000; Sanz et al., 2004)

8. Refractory and relapsed disease

8.1 Arsenic trioxide

Patients who do not achieve cytogenetic remission after induction therapy and/or molecular remission after consolidation are considered to have refractory disease, while those in remission who suddenly have detectable *PML-RARA* by RTC-PCR have relapsed APL. In both situations, salvage treatment is needed and arsenic trioxide (ATO) can induce CR in 85 to 88% of patients, and this can be followed by stem cell transplantation (Soignet et

al., 2001; Soignet et al., 1998). ATO not only induces degradation of the *PML-RARA* fusion transcript, leading to differentiation of malignant promyelocytes, but also leads to the death of "leukemia-initiating cells" (Nasr et al., 2009).
So far reserved for the treatment of refractory or relapsed disease, in addition to some use in patients with contraindications to anthracyclines (Sanz et al., 2009), ATO has and is currently being studied for use in first-line induction therapy alone or in combination with ATRA without any chemotherapy (Hu et al., 2009; Mathews et al., 2006). This, however, has not yet become standard of care.
ATO is usually given at 0.15 mg/kg/day intravenously until hematologic remission or for a maximum of 60 days. The major side-effects of this drug are fluid retention, differentiation syndrome and QT prolongation (Unnikrishnan et al., 2004).

8.2 Other agents

Repeat treatment with ATRA and chemotherapy in refractory and relapsed APL has had disparate success, and other agents that might be of benefit in this setting are still under investigation including gemtuzumab, Hum195 which is an anti-CD33 antibody, sodium phenylbutyrate, and calcitriol.
Of special note, tamibarotene, a synthetic retinoid synthesized by the University of Tokyo in 1984 and 10 times more potent than ATRA, seems to be especially promising. Tamibarotene is approved in Japan for use in relapsed and refractory acute APL, and was successfully used at our institution (University of Texas Southwestern Medical Center) in a patient with relapsed and refractory extra-medullary APL (Naina et al., 2011). Tamibarotene is currently being compared to ATRA for maintenance therapy in the ongoing APL204, a randomized phase III trial of the Japan Adult Leukemia Study Group.

9. Other considerations

9.1 Coagulopathy

Within the first 10 days of treatment, 5-10% of APL patients will develop fatal hemorrhage, especially in the central nervous system (CNS) and lungs (Rodeghiero et al., 1990). This is secondary to a characteristic coagulation disorder combining disseminated intravascular coagulation (DIC) and fibrinolysis that is not well understood. Platelets and cryoprecipitate should be transfused to maintain platelet counts more than 30-50x10^9/L, and fibrinogen level more than 150 mg/dL, respectively (Tallman et al., 2005). ATO and ATRA have both been shown to quickly correct this coagulation disorder, and the initiation of the latter has become a true emergency in any new APL patient. ATRA should be promptly started when APL is clinically and cytologically suspected even if cytogenetic and molecular confirmations of the diagnosis are pending (Sanz et al., 2009).

9.2 Central Nervous System (CNS) prophylaxis

The CNS is the most common site of extramedullary disease and relapse in APL (Evans and Grimwade, 1999), with elevated WBC count > 10x10^9/L being the only significant risk factor in a multivariate analysis (de Botton et al., 2006). There are no guidelines as to the systematic CNS prophylaxis of APL patients with leukocytosis. Groups who include intrathecal chemotherapy in their regimens administer it during consolidation, not during induction when the risk of fatal bleeding is high. ATO crosses the blood-brain barrier and is being

evaluated for use in first-line induction therapy; it is conceivable that such induction regimens will result in lower rates of CNS relapse.

9.3 Differentiation syndrome

Also known as the retinoic acid syndrome or cytokine storm, it is seen in around 25% of APL patients in the first 3 weeks following treatment with ATRA or arsenic trioxide (Vahdat et al., 1994). The differentiation syndrome is caused by the release of cytokines from neoplastic promyelocytes as they differentiate in response to treatment. Usual symptoms include fever, shortness of breath, peripheral edema, pulmonary infiltrates, hypoxemia, respiratory distress and hypotension. Patients can also develop renal and hepatic dysfunction, in addition to pleural and pericardial effusions. The syndrome can be fatal and prompt recognition is vital, leading to the initiation of intravenous dexamethasone 10 mg twice daily until clinical resolution, followed by slow steroid taper. Patients with WBC > $10x10^9$/L are suspected to be at increased risk, and some recommend treating this group prophylactically with steroids (Wiley and Firkin, 1995).

10. Conclusion

Over the last 2 decades, we have witnessed a change in acute promyelocytic leukemia from the most malignant form of AML to the most curable one; a remarkable medical achievement that did not rely on advances in chemotherapy, but rather on molecular targeted therapy in the form of differentiation agents. This innovative approach to the treatment of malignant neoplasms was later emulated by the use of tyrosine kinase inhibitors in chronic myeloid leukemia. The latest scientific breakthrough in APL is the discovery that ATRA and ATO not only induce differentiation but also eradicate "leukemia-initiating cells" or "leukemic stem cells" (Nasr et al., 2009), leading to think that their combination in induction regimens could result in higher rates of prolonged remission and cure. This has opened the door to new clinical trials in APL and a rational that might prove one day applicable in other hematologic malignancies.

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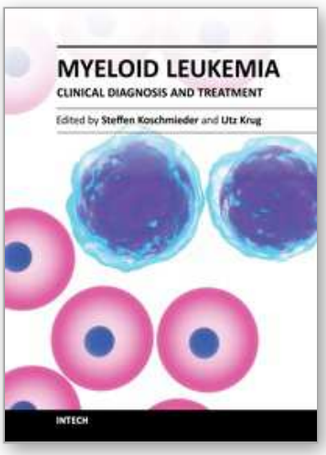

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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and 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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