

New Advances in the Treatment of Acute Promyelocytic Leukemia

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Abstract

Objective: Describe the treatment options of newly diagnosed and relapsed APL. **Induction:** The fusion PML/RAR gene provided the rationale for using all-*trans* retinoic acid (ATRA) as differentiation therapy. The standard approach is anthracycline + ATRA and no ARA-C. **Consolidation:** Anthracycline based chemotherapy, no high dose ARA-C and perhaps no ARA-C. Maintenance seems to be important. Cure with ATRA + chemotherapy increased to 75% from 35% with chemotherapy alone. **Poor prognosis factors:** WBC >10,000, age >55, platelets <40,000 and CD 56 expression. Achieving and maintaining a molecular remission (MCR) i.e. RT-PCR (-) for PML/RAR α expression, is the best predictor for cure. Conversion to PCR (+) will eventually result in relapse. PCR monitoring in the first 2 years and intervention during molecular relapse would be safer than treatment in clinical relapse. Molecular relapses have been treated successfully by ATRA plus BMT. Arsenic trioxide (ATO) or gentuzumab (mylotarg) are also being studied. **Relapse (induction):** Patients after ATRA in first CR are less likely to respond to ATRA reinduction regardless of the time off ATRA and rarely achieve a molecular remission. Single-agent ATO induced in 52 relapsed patients CR of 87% (75% MCR) with low toxicity and no treatment related deaths (U.S. pivotal trial), confirmed in a NCI trial. Induction of relapsing patients with single agent ATO is preferable than ATRA + chemotherapy because the high molecular remission and lower toxicity. **Relapse (Post remission):** No standard approach and the role of chemotherapy is unknown. ATO alone: in the pivotal trial, 9/21 patients had long remissions without other therapy. BMT: Not indicated in 1st MCR. In young patients auto BMT with PCR (-) harvests could be done in subsequent CR. Allo BMT has a higher death rate without overall better results. In the pivotal trial 12 patients were transplanted in CR after ATO alone (9 allo BMT) and 11 still without disease. Possibly allo BMT is safer after a less toxic ATO induction. **Other:** ATO plus ATRA +/- AntiCD33 conjugated with toxin (gentuzumab) or ¹³¹I; Synthetic retinoid (Am80); histone deacetylase inhibitors; oral tetra-arsenic tetra-sulfide and various combinations.

In the last decade, two non-chemotherapy small molecule drugs were discovered that improved the outcome of acute promyelocytic leukemia (APL) at a magnitude that is unparalleled in any other cancer. First, all *trans* retinoic acid, that induces a complete remission by cell differentiation in nearly every newly diagnosed APL patient; when combined with chemotherapy doubled the cure rate to 75% compared to chemotherapy alone. Further, ATRA is the only transcription factor therapy that has become standard in clinical practice, by specifically targeting the aberrant transcription factor that underlies the pathogenesis of this disease [1]. The second improvement was achieved by the discovery that arsenic

trioxide can induce a complete remission in 85% of relapsed APL patient including those who failed ATRA, chemotherapy or stem cell transplantation.

1. Acute Promyelocytic Leukemia

APL is a subtype of acute myeloid leukemia that was recognized as a distinct clinical entity in 1957. The marrow is infiltrated with leukemic blasts and granulated promyelocytes that often contain one or multiple Auer rods. In 1976, the French-American-British Group classified APL as FAB M3 subtype [2,3]. Later a morphological variant of APL was recognized, the M3 variant

(M3) distinguished by microgranular promyelocytes and lobulated nucleoli [5]. Several large cooperative group studies have reported a 5-13% frequency of APL among accrued AML patients [5-7]. A similar range of frequency of APL has also been reported in several series reporting cytogenetic analysis of AML [8-10]. The frequency is been reported to be higher in Latinos in Los Angeles [11-12] Mexico [13] and Peru [14]. APL is mostly seen in patients aged 20-60 with peak incidence at age 40 and is rare in children and the elderly [12]. Clinically, APL is associated with a bleeding diathesis, which usually becomes more serious during the initial administration of chemotherapy, and is attributed to disseminated intravascular coagulation and excessive fibrinolysis. APL is diagnosed without organomegaly and rarely has an antecedent myelodysplastic syndrome. In most cases, patients have a low white cell count but 10-20% are diagnosed with WBC greater than 10,000/cumm, which is associated with a higher mortality rate from bleeding. The immunophenotype of APL is highly specific (HLA-DR-, CD34-, CD15-, CD33+, CD13+)[15,16]. M3v has distinctive clinical features such as relative high white cell count and a higher mortality from severe coagulopathy, with hemorrhage into the central nervous system and/or lungs [17,18].

2. Molecular Biology

In the mid 70th, a unique cytogenetic abnormality was discovered in APL, characterized by a balanced reciprocal chromosomal translocation t(15;17) [19]. In 1990, the t(15;17) translocation of APL was found to result from a breakpoint in chromosome 17 located within the locus encoding the RAR α gene and in chromosome 15 it falls within the PML gene [20,21]. This formed the APL specific fusion gene on chromosome 15 composed of most of the PML gene and RAR α genes traslocated from chromosome 17, expressing of the hybrid PML-RAR α transcript [22].

The PML/RAR α fusion protein gene is involved in the pathogenesis of APL [1,23,24]. Further administration of pharmacological doses of ATRA, the ligand for the normal retinoic acid receptor, induces terminal differentiation of the tumor cells leading to a clinical remission. The M3v bears t(15;17), expresses the PML/RAR α protein, and responds to ATRA treatment. The breakpoint in the RAR α gene has consistently been described in intron 2 while the PML breakpoints may occur in three different sites: intron 6 (called bcr1 or the long form), exon 6 (bcr2 or the variable form), or intron 3 (called bcr3 or the short form) [25-27]. The distribution of the breakpoint sites in the PML gene has been reported in several studies from Europe [25,27,29] and USA [30,31] to be approximately 50-55% for bcr1, 8-20% for bcr 2 and 27-49% for bcr 3. Interestingly we have found in two Latinos APL populations: one from the Los Angeles area (patients from Mexico and Central America) and the other from Peru (South America) that APL patients express a higher rate (73%) of the bcr1 [32]. Although early studies, suggested that bcr3 was

associated with better prognosis, more recent studies larger studies found no statistical significant difference in the outcome between bcr1 or bcr1+2 and bcr3 patients [29,30,33-35].

PML-RAR α expression is also responsible for the dramatic response of APL to ATRA, which is supported by several observations. The leukemic cell respond to ATRA by undergoing differentiation towards mature myeloid cells that eventually die by apoptosis and allow the normal non leukemic marrow to recover. In the absence of the ligand (ATRA), the PML-RAR fusion protein recruits histone deacetylase that mediates transcriptional repression and block differentiation of the leukemic cells. High doses of ATRA that bind to the PML-RAR α fusion protein, cause recruit transcriptional activators with histone acetylase activity that release the block of differentiation [36,37]. Also, ATRA downregulates PML-RAR expression [1,23,38,39].

3. Therapy of Newly Diagnosed APL Patients

3.1. Induction Therapy

APL cells are specially sensitivity to anthracyclines and higher remission rates can be induced with daunorubicin as a single agent, compared to other subtypes of AML. In a prospective randomized trial no difference in the CR rate as found between daunorubicin alone and daunorubicin and cytarabine [40-44].

Initially, APL was treated exclusively with cytotoxic chemotherapy, but once the nature of the characteristic translocation product was understood, the potential therapeutic role of retinoic acid was studied. As early as 1988, investigators in Shanghai reported that treatment with single agent ATRA in resulted 90% in complete remission (CR) (<<dcl, huang, 1988, p567, abstract >> [45] and French Investigators confirmed these clinical results [46]. With 45 mg/kg per day given orally in two divide doses, almost all newly diagnosed APL cases with PML-RAR α rearrangement respond to ATRA. Primary resistant is extremely rare and failures are due to toxicity, mainly hemorrhage and infections. Early in the course of treatment, ATRA resolves the coagulopathy that is a major cause of early death in APL instead of worsening the bleeding when chemotherapy is given. However, bleeding into the brain and lungs remains a problem even with ATRA therapy. The average time to remission is approximately 40 days. A rise in white cell count is commonly seen during the early days of treatment that in some cases can be rapid and reach very high levels. The WBC counts drop to normal as the cells continue to differentiate and the patient enters complete remission [46-48]. In many cases, this is an asymptomatic laboratory finding and treatment with hydroxyurea or leukapheresis to decrease the white count is not required [47,48]. However, several centers use intensive anti-leukemic chemotherapy when the WBC rose above a certain level (see below). Although newly diagnosed APL patients do not show resistance to ATRA, they do not remain in a long term remissions if

maintained on ATRA therapy alone [45,47-49].

The most severe side effect of ATRA is the ATRA syndrome. It occurs in the first month of treatment, occasionally very early in the course of treatment and even immediately after the first dose of ATRA [50-52]. The clinical symptoms are fever, respiratory distress, pleural or pericardial effusion, interstitial lung infiltration on the x-ray. If left untreated it will progress to hypoxia, respiratory failure, and death. In most cases, the syndrome develops in association with the rise in the WBC but some patients had normal counts. Administration of dexamethasone 10 mg IV twice a day as soon as the first symptoms occur will prevent the development of this potential fatal syndrome. Because of the association with hyperleukocytosis, several groups add full dose of induction chemotherapy to the ATRA treatment when an increase in the WBC is seen and the incidence of this syndrome dropped 10% [43,54,55]. Other common side effects are headaches, dry skin and mucous membranes, and some cases bone pain and hypertriglyceridemia. In rare cases, especially in children, pseudotumor cerebri can develop.

The New York group reported that 59 (81%) of 73 newly diagnosed patients achieved a complete remission with ATRA alone [55]. In a European pilot study using the first approach, 25 of 26 (96%) newly diagnosed patients achieved a CR [56]. In a multicenter study of 110 patients in Japan, 89% achieved CR either with ATRA alone or with the addition of chemotherapy [57]. The Japan Adult Leukemia Study Group treated 198 newly diagnosed APL patients with chemotherapy and ATRA and noted that 88% achieved CR [58]. The first randomized trial, the European APL91 study, compared ATRA plus standard daunorubicin/cytarabine induction to the same chemotherapy regimen given alone [58] without a significant difference in the CR rate. Fatal bleedings were observed in both groups but in the ATRA group no primary resistant was noted. In the North American Study, newly diagnosed patients were randomized to induction with ATRA alone or to standard anti-leukemia induction chemotherapy of daunorubicin/cytarabine [51]. The complete remissions rate, mortality and incidence of severe hemorrhage were the same for both groups. Another randomized trial conducted by the British Medical Research Council demonstrated that ATRA has to be given until CR even with chemotherapy [59]. Patients randomized to a short course of ATRA followed by chemotherapy did poorly than patients who received ATRA until CR plus chemotherapy.

Although the CR rate of ATRA and ATRA plus chemotherapy is similar, the latter approach has become the most commonly used approach. One rationale is the possible lower rate of ATRA syndrome compared to ATRA alone. In addition the European, APL93 trial, 413 patients were randomized to receive induction therapy consisting of ATRA plus chemotherapy or ATRA followed by chemotherapy. Both groups of patients received consolidation chemotherapy. Although the CR

rate was not different, in the group receiving ATRA followed sequentially by chemotherapy, the relapse rate at 2 years was statistically significant higher (16%) compared to 6% in the group that received induction with ATRA chemotherapy simultaneously [60].

The special sensitivity of APL anthracycline chemotherapy has established that ATRA can be combined with idarubicin without cytarabine with no reduction in the CR rate. The GIMEMA group in Italy showed that the combination of ATRA and idarubicin given at 12 mg/m² on days 2,4,8,9 (AIDA) induced a 95% CR rate in 253 newly diagnosed APL patients [61,62]. This result was confirmed in the PETHEMA group in Spain that observed CRs in 89% of 123 previously untreated APL patients who received ATRA and idarubicin [54].

3.2. Post-Remission Treatment and Outcome

APL patients must receive two or more cycle post remission consolidation chemotherapy even if chemotherapy was given during induction.

The most striking finding is that ATRA plus chemotherapy given concurrently or after ATRA, resulted in significantly higher overall survival and disease free survival rates compared to their own historical controls treated with chemotherapy before ATRA was introduced [47,57,58,63]. This outcome was confirmed in three randomized trials. In a European APL91 trial, 101 patients were randomly assigned to receive either ATRA followed by daunorubicin/cytarabine or chemotherapy alone [58]. In a recent update at 4 years, both event-free survival and relapse rate were significantly better ($p=0.0001$ for both) among patients who received both ATRA and chemotherapy than among those in the chemotherapy-only arm. At 4 years, 78% of chemotherapy-only patients had relapsed, compared with only 31% of patients who received both ATRA and chemotherapy [64]. The updated analysis of the North American multicenter trial [51,65] reported a 5-year disease-free survival of 30% for 123 patients receiving chemotherapy induction, compared with 64% for 127 treated with ATRA induction. The 5 year overall survival was 45% and 69%. This difference in disease-free survival is due largely to the difference in the relapse rate [51].

The optimal consolidation treatment and the number of cycles, is still unclear but all use anthracyclines. Several approaches have been used in the various studies. Maintenance therapy after consolidation appears to offer advantages and improve outcomes. The optimal maintenance regimen has not yet been defined but more favorable outcomes have been observed when ATRA alone or 6-mercaptopurine/methotrexate chemotherapy with or without ATRA [51,60]. ARA-C may not have a role in consolidation from the entire treatment protocol [66]. In a prospective study, the PETHEMA group treated

APL patient in CR with three consolidation cycles consisting of anthracyclines with not other drug and reported OS 82% and DSF of 78% [54]. In comparison the AIDA Italian group used three cycles of consolidating consisting of identical doses and schedule of the anthracyclines but in each cycle cytarabine or etoposide were include; in both trials the Induction and maintenance treatments were identical. Although these were not a randomized trials the OS and DFS were similar, 87% and 79%, respectively [62].

4. Risk Factors for Relapse

Patients with elevated white blood cell counts, exceeding $10 \times 10^9/L$ at presentation, typically experience a greater risk of relapse after achieving CR compared with patients with lower white cell counts [54,59,60]. <<dcl, chou, 1997, p925, Figure 3 & col 2, par 2; asou, 1998, p83, Figure 4; sanz, 1999, p3019, Figure 2 & col 1, par 2; burnett, 1999, p4131, abstract; fenaux, 2001, p18, col 1, par 3>> Sanz and colleagues developed a simple predictive model to define [34] both WBC and platelet counts and identified three groups: (1) low-risk: WBC $10 \times 10^9/L$ and platelets $>40 \times 10^9/L$; (2) intermediate-risk: WBC $10 \times 10^9/L$ and platelets $40 \times 10^9/L$, and (3) high-risk: WBC $>10 \times 10^9/L$. The differences in DFS for all three risk groups were significant ($p < 0.0001$). Older age and expression of CD56 are also associated with an increased risk of relapse. The cure rate of patients with WBC $>10,000$ is approximately 60% and different approaches should be investigated to improve their outcome. In patients with WBC $>10,000$ ATRA is given with Idarubicin the first day of induction while in other patients the treatment begins with ATRA for 2-3 days before chemotherapy. Cytogenetic abnormalities in addition to t(15:17) have not been associated with worse outcome.

4.1. Minimal Residual Disease

Reverse transcriptase-polymerase chain reaction (RT-PCR) is used to test for the presence of the PML-RAR α fusion transcripts in patients with APL in remission to detect minimal residual disease. Persistence of negative PCR for PML-RAR α expression is associate cure and the goal of treatment is a molecular remission (i.e. RT-PCT negative). Patients with persistent or recurrent positive RT-PCR assays will eventually relapse [27,67]. Intervention in this setting of minimal tumor burden rather than awaiting clinical relapse, would be safer, as the risks for the more serious disease and treatment-related complications are minimized. This could improve the likelihood of prolonged complete remission or possibly cure. Therefore, it is recommended that the bone marrow of all patients with APL be monitored every 3-4 months by RT-PCR testing for evidence of molecular relapse during the first two years after achieving CR. Two positive PCR testing within one month is considered as molecular relapse. The optimal approach in molecular relapse to re-induce a molecular remission

and possibly increase the cure is not yet clear. ATRA followed by stem cell transplantation has been found useful in a small number of patients [68]. Other approaches such as high dose cytarabine, arsenic trioxide or antiCD33 antibodies are under investigation.

5. Treatment of Hematological Relapse

Induction of remission in relapsed APL has been studied on smaller number of patients and no randomized were done [69]. Several approaches have been used: chemotherapy, ATRA+/-chemotherapy and trisenox [the FDA approved form of arsenic trioxide]. Unconjugated anti-CD33 or anti-CD33 conjugated with immunotoxin [Gentuzumab ozogamycin, mylotarg] have activity in APL and are currently being investigated in clinical trials.

5.1. Treatment with ATRA in ATRA Naive Patients

In a retrospective analysis by Cortes et al, 48 patients in first relapse who had never received ATRA achieved a 56% CR rate with combination chemotherapy alone with a short disease-free survival [DFS] of 9.7 months and survival of four months [70]. In the same report a higher CR rate of 82% was found when ATRA was combined with chemotherapy as salvage therapy in 17 ATRA-naive chemotherapy relapsed/refractory APL patients (CR rate of 87% in the 13 of the 15 patients in first relapse) [70]. Neither duration of CR (9.3 months) nor overall survival (9.3 months) was significantly different for ATRA-treated patients compared with their chemotherapy historical controls. In another study the CR rate was 92% with ATRA to chemotherapy in ATRA nave first relapses but the DFS was similar to chemotherapy alone [71].

It is still possible to achieve a high second CR of 70-100% with ATRA alone in ATRA nave patients, but the DFS is shorter than that of newly diagnosed patients [47,69,72].

5.2. Re-treatment with ATRA

Nowadays almost all relapsing patients would have already received ATRA and it would be unusual to see an ATRA nave patient. Warrell and colleagues report that none of 10 patients who relapsed while taking ATRA maintenance responded to dose escalation of ATRA [72]<<dcl, warrell, 1994, p930, col 2, par 2 >>. The same group reported 3 of 10 patients who had stopped ATRA between 4 and 25 months before relapse achieved CR with a second ATRA induction. <<dcl, warrell, 1994, p931, table 1>> A group from Japan noted that CR was achieved by only 3 of 17 patients retreated with ATRA following relapse after ATRA-induced first CR. and in this report, the likelihood of CR with ATRA reinduction had no consistent relationship to the duration of the ATRA-free interval <<dcl, tobata, 1997, p970, col 2, par 1>> [73]. In contrast, in a small cohort from the European APL study, all 13 first relapsed patients achieved a CR

with ATRA alone [71]. Taking these results together, about 20% of APL patients previously treated with ATRA appear to retain sensitivity to treatment with this agent [73] <<dcl, tobita, 1997, p970, col 2, par 1>>. The prevailing concept that patients who have been off ATRA for more than 1 year, are more likely to be reinduced with the same drug, is not well established. Although, the European cohort of patients were off treatment for more than 6 months, in the other studies, no correlation was found between the response to reinduction with single agent ATRA and the time off the drug [72-73]. Single agent ATRA rarely induces PCR negativity, cannot maintain the remission and therefore is given with chemotherapy. The combination of ATRA and chemotherapy can induce a CR rate of 95% as reported by the European group with a DFS of 3 years of 54% [71]. This survival is compounded by the fact that 70% of the patients received a stem cell transplant in second CR.

5.3. Arsenic Trioxide

Arsenic trioxide has initially shown in Chinese studies remarkable efficacy in the treatment of APL with an overall remission rate of 52%- 85% in refractory or relapsed patients [75-77]<<dcl, zhang, 1996, p439, abstract>>.

In a larger US multicenter study, 40 relapsed APL patients were treated with arsenic trioxide 0.15 mg/kg until CR or a maximum of 60 days [31]. All patients in this trial had already received treatments with an anthracycline and ATRA before relapsing. Thirty-four patients (85%) achieved complete remission. The median time to clinical CR was 59 days although a bone marrow remission was seen after a median of 35 days. Response rates were similar in all age groups, in patients after one or multiple prior regimens and in patients with prior BMT. No relation was found between the CR rate and time from last ATRA treatment. When the results for these 40 patients were combined with those of the 12 patients in the pilot trial, an overall response rate of 87% was observed; 45 of the 52 patients achieved CR, and 78% became negative to RT-PCR<<dcl, soignet, 2001, p3855 col 1>> for the PML-RAR one or two cycles of arsenic trioxide, respectively [31]. The two-year overall survival and relapse-free survival estimates for these 52 patients 63% and 49%, respectively. The two-year overall survival and relapse-free survival estimates for patients treated in first relapse were 77% and 58%, respectively. The high CR rate in relapsed APL with the same dose of trisenox was confirmed in 57 patients studied in a national NCI compassionate trial [CR = 74%] [78] and in 12 patients in a single institution, M.D. Anderson [CR = 100%] [79]. In the latter study, 75% achieved a molecular CR with single agent trisenox.

Arsenic trioxide is generally well tolerated. Frequently occurring adverse effects include nausea/vomiting, fatigue, headache, diarrhea, hypokalemia, hyperglycemia, rash, edema and neuropathy. Leukocytosis, which re-

solved with continuation of arsenic trioxide therapy, was seen in half of the patients in the U.S. multicenter trial but only during induction. Of more importance is a pulmonary complication the APL differentiation syndrome occurring in 25% of the patients, all with leukocytosis. Prompt treatment with dexamethasone prevented its progression to respiratory failure and arsenic trioxide could be continued. No chemotherapy was given to reduce the WBC count. A review of 949 ECGs from 99 patients treated in clinical studies with trisenox the FDA-approved form of arsenic trioxide, revealed QTc prolongation in 69 percent of patients. However, within the >470 clinical trial patients and >400 post-marketing patients who have received trisenox no arrhythmias, symptoms, sudden deaths or cardiac deaths related to arrhythmia have occurred.

Despite the absence of a clinically relevant safety event linked to the QTc prolongation vigilant monitoring of ECGs and serum potassium and magnesium levels, which should be maintained above 4 and 2 respectively, is important, during treatment. Adding one or both of the electrolytes will shorten the prolonged QT.

The impressive efficacy of arsenic trioxide, as well as its manageable, non-chemotherapy side effect profile, have established arsenic trioxide as the treatment of choice in patients with first and subsequent relapsed APL. Single agent arsenic trioxide would be preferable for induction over ATRA even in patients who are off the drug for more than 1 year. The CR rate with ATRA alone is not consistently high as the results with arsenic trioxide; there is no proven relationship between the duration of first CR off ATRA and response; PCR negativity with single agent ATRA is very rare and the drug cannot be used as single agent and always requires intensive and toxic chemotherapy. Because the much lower toxicity of arsenic trioxide and a similar CR rate, it would still have advantage over chemotherapy with or without ATRA.

5.4. Post-Remission Treatment in Arsenic Trioxide CR

Once the patient is induced into complete remission with arsenic trioxide, the specific post-remission approach is less clear. Maintenance with single agent ATRA is not effective, since it results in the development of resistance. Maintenance with trisenox may be used. No studies have presenting the effect of chemotherapy in these patients. In a retrospective analysis, of the U.S. trisenox pivotal trial, 21 patients received maintenance treatment with arsenic trioxide alone and nine of them are alive without a recurrence for at least 2.5 years. Eight of these patients required at least 3 cycles of trisenox. Several ongoing trials are studying the use of ATRA plus arsenic trioxide with or without gemtuzumab ozogamycin (mylotarg)

5.5. Hematopoietic Stem Cell (HSC) Transplantation

Because of the high cure rate HSC transplantation is not recommended in first CR especially in PCR negative patients. The role of HSC in APL during the

ATRA era is reported from large registries like the European BMT registry, the International Bone Marrow Transplantation Registry and from a small cohort of 22 patients reported by the European APL group [71,79,80]. The results reveal a low relapse rate with allogeneic transplantation, [15% out of 127 patients in the EBMT registry and one of 11 in the European APL group. However, allogeneic transplantation was associated with very high toxicity, [39% treatment related mortality in the EBMT registry]. In the European APL group 8 of 11 patients, [73%] died from treatment related complications. This high death rate was attributed to the intensive chemotherapy that was administered as part of the induction treatment prior to transplantation. Results of autologous transplantation in APL were reported by EBMT in patients transplanted between 1993-1999 and showed a higher relapsed rate of 44% or in the European APL group, 3 out of 22 patients. However, autologous transplantation was safer with a treatment related mortality of 25% in the EBMT registry and 9% in the European APL group. Overall, the outcome appeared to be similar or even better with autologous transplantation: DFS at 3 years of 45% [EBMT] and 77% [European APL group]; overall survival at 3 years, 48% [EBMT] and 79% [European APL group]. In a small group of patients it appears that the best results are with autologous harvest that were PCR negative for PML/RAR gene expression [82]. In a retrospective analysis of the U.S. pivotal trial, 12 patients were transplanted in CR after arsenic trioxide alone; 9 were allogeneic. After follow of 2 years, 11 patients are still alive without disease. This is in contrast to the very high mortality rate when BMT follows intensive chemotherapy. The low toxicity of arsenic trioxide may make allogeneic transplantation safer. This needs to be confirmed in more patients. In summary, arsenic trioxide maintenance can still be used while following the PCR status and adding treatment in patients converting to PCR positive. Younger patients should receive 2 or 3 cycles of arsenic trioxide would probably benefit from a transplantation procedure, since the role of maintenance with arsenic trioxide alone is not yet clear. In the absence of additional data, auto transplant may be preferable even in patients who have an HLA identical donor if the harvest is PCR negative. This recommendation is based on the high death rate with allogeneic transplantation and no evidence that the overall results are better than auto transplantation. If the possibility that the low toxicity of arsenic trioxide makes allogeneic transplant safer is confirmed, then it may be a better choice when a matched sibling is available. More information is needed on autologous and allogeneic transplantation after arsenic trioxide induced remission, as well as the question of administration of arsenic trioxide post auto transplantation.

6. Emerging Therapies

A number of new agents were found to be active in APL. Several clinical are currently investigating them as

single agents or in combination with other drugs with the main objectives to reduce the relapse rate in high risk new diagnosed, in second or subsequent CR, convert PCR positive CR patients to a molecular CR as well as reducing or eliminating the used of cytotoxic chemotherapy.

6.1. Anti CD33 Antibodies

CD 33 antigen is found on the majority of AML cells including APL and antibodies to this antigen have been used to target therapy to these cells. The optimal treatment of these agent are currently being tested in a variety of clinical trials.

6.1.1. ¹³¹I-M195

This a radioactive labeled mouse ant CD33 antibody that binds CD33 was administered to seven patients in a second complete remission attained with ATRA. Six patients were PML/RAR positive after ATRA and two converted to PCR negative. This approach was limited by significant myelosuppression and development of human antimouse antibodies [83].

6.1.2. Native Humanized Anti-CD33 (HuM 195)

This antibody was found to have activity as single against minimal residual APL. Twenty-four newly diagnosed APL patients induced into CR with ATRA alone and were still PCR positive received HuM195; 12 of them (50%) converted to PCR negative before receiving any further therapy [84]. The patients in this study later received chemotherapy. HuM195 alone or in combination with other agents such as arsenic trioxide may reduce or even eliminate the need consolidation with chemotherapy.

6.1.3. Calicheamicin Conjugated Humanized Anti-CD33 (gemtuzumab ozogamycin, mylotarg)

This agent has activity in heavily pre-treated relapsed APL [85]. However, the experience using this drug in APL is still limited and as opposed to arsenic trioxide and has more toxicity with long myelosuppression. Recently Estey et al [86] reported that the combination of two doses mylotarg plus daily ATRA induced a CR in 14 of 16 newly diagnosed APL patients with WBC < 30,000 and no idarubicin. This result is similar to that of ATRA plus idarubicin. A molecular CR was achieved in all the 12 patients tested. Patients continued with the same monthly mylotarg plus daily ATRA as consolidation and in a short follow up, none of those tested have converted to PCR negative.

6.2. Differentiating Agents

6.2.1. Histone deacetylase inhibitors

Modulation of histone acetylation affects repression

and derepression of gene transcription. Histone deacetylase inhibitors markedly influence gene transcription in APL cells in response to ATRA. These agents restore ATRA responsiveness in ATRA-resistant APL cell lines, allowing ATRA to activate gene transcription via the RAR moiety [87]. <<dcl, lin, 1998, p811, abstract, p813, col, 1, par 1>> Warrell and colleagues reported that treatment with the histone deacetylase inhibitor phenylbutyrate restored ATRA sensitivity to an ATRA-resistant patient with APL who had experienced multiple relapses, inducing complete clinical and molecular remission [88].

6.2.2. Synthetic Retinoids

Am80 is a synthetic retinoid with several potential advantages over ATRA: it is 10 times more potent than ATRA in inducing differentiation in vitro, and is markedly more stable. Among 24 APL patients who relapsed after ATRA therapy, 14 (58%) achieved a second CR with Am80 alone [89].

6.3. Tetra-arsenic Tetra Sulfide

Arsenic trioxide can only be administered orally. In a recent report from China used Tetra-arsenic tetra sulfide (As₄S₄) was purified from form Reaglar, a mined ore that had been used for centuries in Chinese traditional for several disease [90]. The pure As₄S₄ is rapidly absorbed after oral administration from the intestinal tract and was found to be highly effective in APL with minimal toxicity. Single agent As₄S₄ induced a hematological CR in all 19 newly diagnosed and 7 first relapsed APL patients with a molecular CR of 87% and 71% respectively. Further, 35 of 44 patients with PCR positive hematological CR converted to a molecular remission.

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