The evolving role of stem cell transplantation in acute promyelocytic leukemia

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Abstract
The availability of several highly effective agents in acute promyelocytic leukemia (APL) including all-trans retinoic acid (ATRA), arsenic trioxide (ATO) and anthracyclines, has transformed this once highly fatal disease into the most frequently curable acute leukemia. While it is firmly established that neither autologous nor allogeneic stem cell transplantation (SCT) are indicated in first remission of the disease, and that patients relapsing after ATRA-containing regimens should be treated with ATO, controversy remains on the selection of the most appropriate consolidation therapy, and in particular on indications for transplantation after second remission. Owing to the lack of randomized comparative studies and the very limited number of relapses, consolidation strategies should be based on several clinical and biological criteria and rely on both available reported experience and published recommendations. These criteria include age and performance status, first remission duration, donor availability, and minimal residual disease status. In this article, we review current recommendations and controversial issues related to use of SCT in APL.

Learning goals
At the conclusion of this activity, participants should be able to:

- describe the available treatment options for patients with acute promyelocytic leukemia in first relapse;
- define the clinical and biological criteria for selecting autologous or allogeneic stem cell transplantation in APL in second remission or beyond;
- describe the available therapeutic consolidation options for patients in second remission or beyond who are ineligible for transplantation.

APL, from highly fatal to highly curable

Over the past two decades, modern treatment with simultaneous all-trans-retinoic acid (ATRA) and anthracycline-based chemotherapy (CHT) has transformed acute promyelocytic leukemia (APL) from a rapidly fatal into a highly curable disease. In fact, more than 80% of patients receiving this combination have been reported to become long-term survivors in large multicenter studies.[1] In addition, excellent outcome results have been reported in APL using arsenic trioxide (ATO) combined or not with ATRA and CHT. Initially shown to be very active in patients relapsing after ATRA-containing regimens, ATO has been tested in several pilot studies in the front-line management of the disease with promising results.[2-5] Moreover, very recent results of a prospective randomized study indicated that combined ATO and ATRA is at least as effective as ATRA and CHT for patients with nonhigh risk disease (commonly defined as those with WBC at diagnosis <10x109/L, and accounting for approximately 75% of cases).[6] While the latter trial results will likely change the standard of care in front-line therapy (i.e. favoring the use of ATO+ATRA instead of ATRA+CHT), they also help reinforce the concept that APL is a highly curable disease in which targeted drugs and/or limited use of conventional CHT are likely to eradicate the disease.

No role for stem cell transplantation in APL patients in first remission

Based on the availability of the aforementioned highly effective agents in the front-line management, there is a general expert consensus on recommending the use of stem cell transplantation (SCT) in APL only after second or subsequent remission.[1] In this respect, it is worth emphasizing that no particular single (or even combined) features associated to slightly inferior prognosis in patients treated with standard ATRA and CHT should justify the use of SCT in first remission. In fact, outcomes in patients showing these reportedly unfavorable features, including elevated WBC counts at diagnosis.[7] CD56 expression,[8] or FLT3-ITD mutation,[9] still remain considerably good. In addition, the chances of achieving second remission with ATO in relapsed APL are extremely high (approximately 85-90%) and repeated ATO given for re-induction and consolidation is able to induce molecular remission in almost 80% of patients treated at relapse.[10,11] Based on these considerations, it should be firmly restated that neither allogeneic SCT (ASCT) nor autologous SCT (AuSCT) have any role in APL in first remission. In the following paragraphs, we will review the current recommendations for transplantation as a consolidation strategy for APL patients in second remission or beyond.

Consolidation options for APL patients in second complete remission

Although most patients relapsing after front-line therapy reported to date had received the standard ATRA and CHT, it is likely that this scenario will change in the near future. In fact, an increasing number of relapses are expected to be reported in patients treated with CHT-free approaches such as ATO +/- ATRA. This is due to a growing interest in the use of the latter approach. In principle, relapsing patients who have never been exposed to CHT should receive the standard ATRA plus CHT for re-induction and consolidation, in parallel with investigating their transplantation options. However, data on the outcome of patients relapsing after ATO who are rescued with ATRACHT followed by SCT are not currently available. For patients who relapse after the standard front-line treatment of ATRA plus chemotherapy, re-induction with ATO is recommended followed by one consolidation cycle of the same agent combined with ATRA.[1,11,12] There is no current consensus on the best option to further consolidate remission after ATO. The very low number of relapsing patients treated with the current standard treatment has made randomized studies comparing different strategies including ASCT, AuSCT, prolonged ATO with or without ATRA or chemotherapy unfeasible. In addition, patients in most reported studies were not systematically monitored for molecular status pre- and post-SCT. Consequently, it is difficult to establish recommendations based on the impact of SCT and other consolidation options in patients included in these studies. Selection of the successive consolidation strategy after ATO and ATRA will depend on a number of variables including patient's age and performance status, duration of first remission, donor availability and minimal residual disease (MRD) status after salvage therapy.[1,11,12] It is widely recognized that AuSCT is considered for patients achieving second molecular remission, i.e.

those who test PCR-negative for the disease-specific PML/RARA fusion gene in their marrow after consolidation, with such tests being performed in highly specialized reference laboratories. Autologous SCT is notoriously associated with lower morbidity and mortality as compared to ASCT and can represent a convenient and effective option for patients with late relapse who achieve second molecular remission. As to the definition of early versus late relapse, and consequently of short versus prolonged first remission duration, here again there is no definitive consensus. Because most standard ATRA plus chemotherapy regimens include prolonged maintenance for two years, we propose that early relapse is considered as that occurring within two years of achieving remission, although this definition may be somewhat arbitrary. Allogeneic transplant is still an effective therapy and a valid treatment option, especially in fit patients at higher risk of subsequent relapse who have a suitable donor. These include patients with short first remission duration (<2 years) and patients who do not achieve a second molecular remission after 2 cycles of ATO+/-ATRA. Prolonged ATO is a viable alternative for patients unfit for a transplantation procedure, or as a bridge during donor identification.[1,13] It remains uncertain as to whether prolonged ATO +/- ATRA can produce long-term remission in APL patients with late relapse, although a single experience of a limited series suggested that a high proportion of patients receiving this treatment strategy may achieve another long-term remission.[13] An algorithm with recommended consolidation options after second CR and criteria for selecting them is illustrated in **Figure 1**.

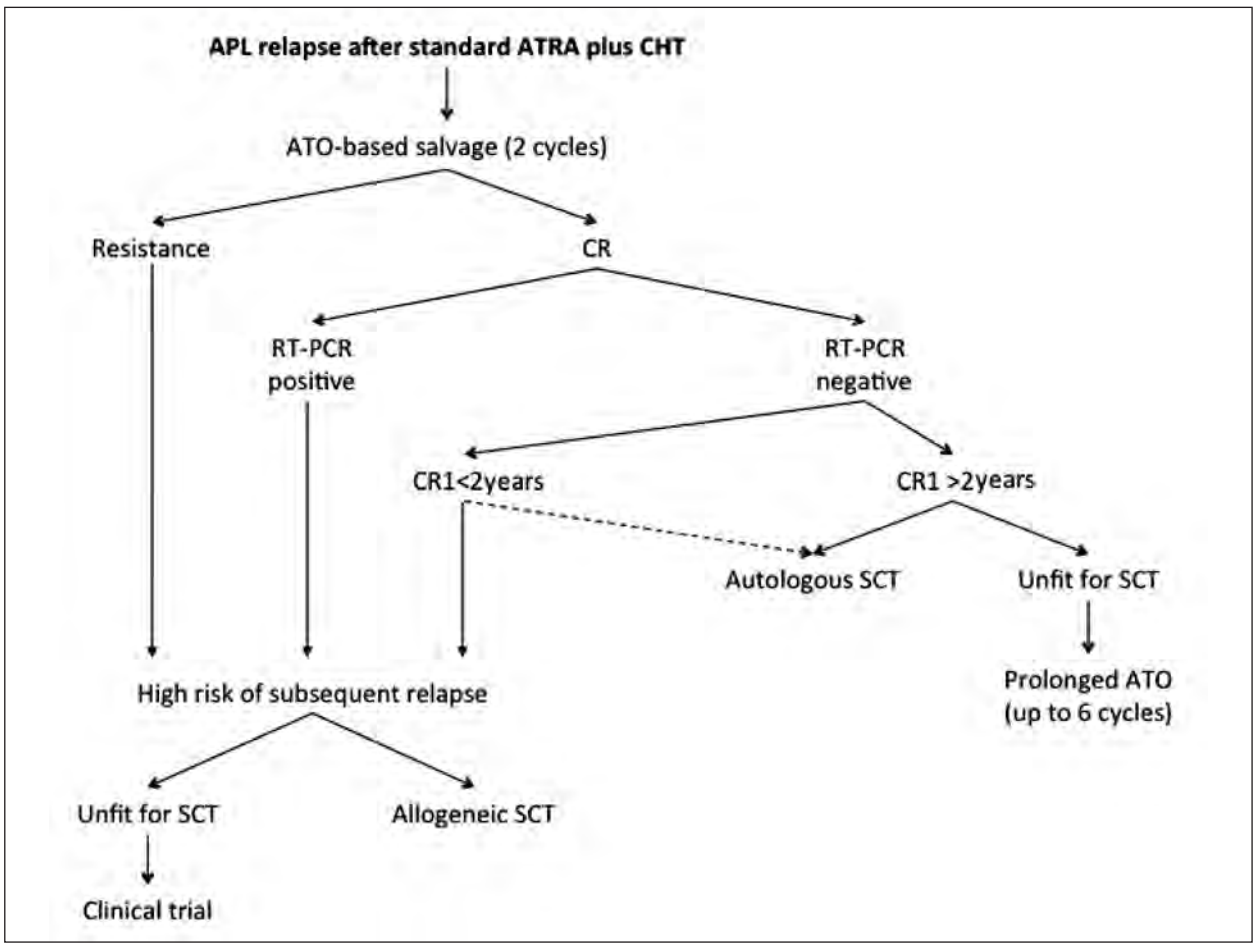

Figure 1: *Therapeutic options for APL patients in second CR. Molecular status for PML/RARA after consolidation and CR1 duration are important factors for the choice of successive options. These may include autologous or allogeneic SCT and prolonged ATO+/-ATRA cycles for patients unfit for an SCT procedure. For patients with molecular CR and CR1 duration under two years, the choice between autologous or allogeneic SCT may also vary based on the type of available donor and clinical parameters (e.g. age, PS) with impact on TRM.*

The following review is organized in sections based on reports comparing results of consolidation with and without stem cell transplantation, consolidation with autologous versus allogeneic transplantation, and reports of consolidation with ATO alone or in combination regimens in patients not eligible for transplant.

Reports of consolidation with autologous and allogeneic stem cell transplantation

Although no prospective randomized trials have been reported, a number of studies compared the role of autologous or allogeneic SCT in APL patients in second remission. Some of these studies documented a similar or even better outcome with autologous than with ASCT. A recurrent observation reported in these retrospective analyses is that transplant-related mortality (TRM) of ASCT hampered a possible OS benefit related to the graft-versusleukemia effect in reducing subsequent relapses. Among these studies, the European Bone and Marrow Transplant (EBMT) group evaluated the role of either AuSCT or ASCT in a large number of patients treated in the ATRA era. In this registry study, patients in CR2 achieved a better leukemia-free survival after ASCT compared to those receiving AuSCT (59% vs. 51%). However this benefit was at the expense of increased TRM (24% vs.16%).18 This study lacked information about MRD prior to and following transplant. We reported a single center study on the outcome after ASCT in 17 patients treated after second or subsequent CR for whom pre-transplant MRD assessment was available. We documented a significant anti-leukemic effect of ASCT even in patients with advanced disease including those with pre-transplant evidence of MRD.19 All patients with MRD positive disease prior to transplant achieved molecular remission after transplant, although the response was less prolonged in more advanced cases. The 10-year actuarial probabilities of OS and DFS were 53% and 46%, respectively; however, TRM was high (32%).19 Studies that evaluated prognostic factors for subsequent relapse after SCT showed that the duration of first remission and the achievement of second molecular remission prior to transplant are associated with post-transplant outcome. [16,19-22] The relevance of pre-SCT MRD status is well established in the autologous transplant setting. Meloni et al. prospectively monitored MRD status of 15 patients who received autologous transplantation in second remission. Six of 8 patients who received PML/RARA-negative marrow achieved prolonged clinical and molecular remissions (median 28 months; range 15-60 months). In contrast, all the 7 patients transplanted with positive MRD relapsed at a median time of five months (range 2-9 months) from transplant.[21] Similarly, the European APL group retrospectively evaluated the outcome of patients who underwent autologous or allogeneic SCT after second complete remission.[16] EFS and OS were significantly better in the autologous setting. Moreover, when the analysis was limited to patients in molecular remission, the 7-year EFS and OS improved to 77% and 75%, respectively, compared to 52.2% and 51.8% in the allogeneic group. Transplant-related mortality was 7% compared to 39% in the autologous and allogeneic settings, respectively.[16] The results from using AuSCT were comparable to those reported by a CALGB study on AML that included 12 APL patients in second complete remission. The 5-year DFS and OS were both 67%.[22] Two other small studies support the use of autologous transplant in patients who achieve a second molecular complete remission.[20,23] The earlier one reported that longterm remission after either allograft or autograft is associated with eradication of PML-RARA positive cells, and that continued positivity predicts subsequent relapse.[20] The more recent one showed that 11 of 13 patients who received autologous transplants while in second molecular remission were alive.[23] Ten patients in this latter study were in sustained molecular remission after a median follow up of 25 months with no TRM.[23] Together these studies suggest that, for APL patients who had a long first remission duration and are in second molecular remission, autologous transplantation is an effective approach for a second lengthy remission.[16-18,20,21,23] We recently evaluated the role of allogeneic transplant in patients with advanced disease (CR2 or beyond) treated in the era of ATO. This study included 31 patients (15 CR2, 16≥ CR3) transplanted in 4 Italian institutions. At time of transplant, 16 patients were MRD positive and 15 were negative. The 4-year overall survival was higher for patients transplanted in CR2 and for MRD negative patients (62% and 64%, respectively) compared to patients transplanted in CR3 or over and positive for MRD (31% and 27%, respectively). MRD status prior to transplant was associated with significantly

better DFS and the rate of relapse was higher in patients transplanted with RTPCR-positive disease.[24] The 4-year cumulative incidence of TRM was 19.6% in this series including advanced disease cases and 7 haploidentical transplants.[23] This improvement may reflect recent advances in transplant supportive measures, wider use of peripheral blood stem cells as well as better haploidentical transplant modalities.[25] In conjunction with other reported series, this study confirms that allogeneic transplant continues to be an effective therapeutic option in relapsed APL patients who are eligible for this treatment policy.

Consolidation reports of ATO alone or in combina tion regimens in patients not eligible for transplant

Given the exquisite efficacy of ATO in APL and the possibility of accurately monitoring response to therapy and re-emerging MRD through PCR analysis, prolonged therapy with ATO-based regimens with or without ATRA may be considered in patients unfit for transplant. Durable molecular remissions were reported in 8 of 9 patients (median CR duration, 25 months) treated with prolonged post-remission therapy consisting of four courses of ATO and seven shorter courses of ATRA. All patients in this recent report had late relapses prior to SCT rescue (at a median time of 1.9 years; range 1-7 years), all except one were treated for molecular relapse, and all were closely monitored for MRD.13 However, this experience was limited to only a few patients, and the identification of patients with low risk of subsequent relapse after first disease recurrence remains challenging.

Conclusion

Recommendations and indications for remission reinduction and consolidation in APL patients with APL relapse are evolving because of the changing scenario in front-line therapy. ATRA-ATO or ATRA-CHT are the standard approach for patients relapsing after chemotherapy- based or ATO-based treatment, respectively. First consolidation after re-induction with further ATO or CHT is recommended with the aim of achieving second molecular remission. All patients must be tested after consolidation for MRD status in experienced laboratories of reference. The choice for further consolidation will be taken in consideration of first remission duration, the quality of remission (molecular vs. hematologic only), patient age and performance status, and donor availability. Autologous SCT can be recommended for patients with prolonged (>2 years) first remission who test negative for MRD after 2 cycles of ATO-based therapy, while patients ineligible for SCT can continue ATO for consolidation and maintenance with close monitoring of MRD. Patients who fail to achieve first complete molecular remission, those who had short first remission, or those who test positive for MRD after ATO induction and consolidation, should be considered for allogeneic SCT if a suitable donor is available. Patients who are candidates for allogeneic SCT should be sent to transplant without delay once they achieve molecular remission.

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