Autologous Stem Cell Transplantation for Patients with Acute Promyelocytic Leukemia in Second Molecular Remission

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Abstract. *Relapse still occurs in approximately 20-30% of patients with acute promyelocytic leukemia (APL) and, after achievement of second complete remission (CR), the optimal strategy is still controversial. We describe therapeutic results from a series of 13 patients autografted in second molecular remission (MR) by a molecular negative apheresis product. In all patients, the disease was confirmed at the molecular level and all had received the GIMEMA/AIDA protocol, achieving molecular remission at the end of consolidation. Relapse was hematological in 12 cases and molecular in one. After consolidation with chemotherapy, all patients achieved MR and received a further course plus granulocyte-colony stimulating factor as mobilizing therapy. A median of 7.6×10^6 (range 2.7-10) CD34-positive cells/kg were collected. In all cases, molecular evaluation of the apheresis product was negative for the promyelocytic leukemia/retinoic acid receptor alpha gene. No case of transplant-related mortality was recorded. No maintenance or consolidation therapy after autologous stem cell transplantation (ASCT) was given to any patient. After a median follow-up of 25 months from ASCT, 10 patients are alive in sustained MR, while two relapsed after ASCT and died in the setting of refractory disease; one patient achieved a third CR and is waiting for allogeneic SCT. These results suggest that ASCT performed with a molecularly negative graft in APL patients in second MR offers a valid chance for achieving a cure. Such an approach should also be considered in relapsed patients with an HLA-compatible donor, namely in those with a first CR lasting more than one year or in unfit or elderly individuals.*

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Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) with peculiar morphological, cytogenetic and bio-molecular characteristics (1). Cytogenetically, APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, *i.e.* t(15;17)(q22;q21), which results in the fusion between the promyelocytic leukemia (*PML*) gene and retinoic acid receptor (*RARa*) gene (2). Because the efficacy of differentiation treatment based on retinoids and/or arsenic derivatives is strictly dependent on the presence of the *PML-RARa* fusion gene in leukemia cells, genetic confirmation of this specific lesion is mandatory in all cases (3). In addition, the hybrid gene is extremely important for the monitoring of therapeutic results, APL being the only AML subtype in which molecular remission (MR), defined by the absence of the leukemic transcript, represents the best indicator of therapeutic efficacy (4).

The treatment of APL represents a paradigm of therapeutic success in clinical hematology, in that more than 90% of patients achieve complete remission with over 70% cure rate (5). Notwithstanding, there are still a number of issues that are open for investigation, including reduction of early hemorrhagic death, minimization and eventually elimination of chemotherapy in low intermediate risk patients and optimal management of relapse, which still account for 5-30% of cases (6-8). Relapse is almost exclusively limited to patients with high-risk disease at presentation and approximately 3%-5% of APL patients develop extramedullary relapse, involving in most cases the central nervous system, but also other sites (9, 10). Finally, a small group of patients (<3%) experience isolated molecular relapse. While there is general agreement on the role of arsenic trioxide (ATO) as treatment of choice in first relapse (11,12), the role of hematopoietic stem cell transplantation after second CR achievement is still the object of controversy (13). Retrospective data analysis of adult patients who had relapsed and were reinduced with all-*trans* retinoic acid -(ATRA) and/or arsenic trioxide (ATO)- based regimen suggest that in individuals who achieve MR, autologous stem cell transplantation (ASCT) is an effective mode of consolidation therapy, with an event-free

survival (EFS) >60% (14-16). In contrast, allogeneic SCT is associated with high treatment-related mortality (TRM) and generally should be reserved for individuals who fail to achieve MR at the end of consolidation therapy and, possibly, those with a very short duration of first CR (17, 18). Although good results have been achieved using SCT, the role of transplant is uncertain, since it is possible that long-term remissions can also be achieved with multiple courses of ATO and/or gemtuzumab ozogamicin (19-22). However, the superiority of ASCT *vs*. consolidation with further ATO courses was confirmed in a recent study on a series including 37 patients with relapsed APL (23). In this study, we describe the clinical characteristics and treatment results from a series of 13 consecutive APL patients autografted in second MR by a molecular negative apheresis product. All patients had relapsed after initial treatment including ATRA and chemotherapy.

Patients and Methods

All 13 patients with APL autografted in first relapse after initial treatment with a conventional ATRA-chemotherapy based regimen (AIDA) between January 2003 and December 2007 were included in this analysis. The median age of patients was 39 (range 18-69) years, 7 patients were male. All patients had received as induction the GIMEMA/AIDA protocol, for which details have been previously described (24). At diagnosis, according to the classification criteria of Sanz *et al*. (25), 2 patients were classified as being at low risk, 5 as at intermediate risk and 7 as at high risk. Morphologically, 8 patients had classical APL, while 5 were diagnosed as APL variant (M3v). One patient developed APL after treatment of multiple sclerosis with mitoxantrone. Ten patients were treated in hematological relapse, three in molecular relapse defined as two consecutive positive RT-PCRs obtained 1 month apart in patients achieving MR (3). The t(15;17(q22;q21) translocation was found in 11/11 evaluable patients, as a unique chromosomal abnormality in 10, with additional chromosomal abnormalities in one). Two patients, in whom cytogenetic analysis was unsuccessful, had molecular positivity for *PML–RARa* gene. At the molecular level, 9 patients showed positivity for BCR1 and 4 for BCR3. In all patients, immunophenotypic analysis, performed as previously described (26), confirmed the diagnosis of APL. At the end of consolidation, performed according to the GIMEMA/AIDA protocol, all patients had achieved hematological and MR. The median duration of first CR was of 18 (range 5-38) months; 7 patients relapsed after more than 12 months from CR1 achievement, 6 after less than 12 months. In all patients red cell concentrates were given to maintain the Hb level >8 g/dl, while platelet concentrates were administered to keep a platelet value $>20\times10^9$/l. Disease-free survival (DFS) was defined as the time from CR achievement to relapse or death from any cause, overall survival (OS) as the time from diagnosis until death from any cause. DFS and OS were calculated by Kaplan–Meier method (27).

Results

Depending on the period of observation and the attitude of the caring institution, treatment of relapse consisted of: ATO (9 patients), ATRA (3 patients), intermediate dose cytosine-arabinoside (ARA-C) plus mitoxantrone (1 patient). After achieving hematological CR, all patients were consolidated with chemotherapy based on high-dose ARA-C, *i.e*. 3g/m^2 every 12 h on days 1 3 5, (4 patients) or intermediate-dose ARA-C (1.5 g/m^2 on days 1 to 5) plus mitoxantrone at 10 mg/mq on days 3-5 (8 patients). In all patients MR was documented. A further course of chemotherapy including intermediate-dose ARA-C plus mitoxantrone was given to all patients in order to perform additional *in vivo* purging of minimal residual disease, as well as to induce mobilization of peripheral blood stem cells (PBSCs). All patients did successfully mobilize PBSCs (median CD34$^+$ cells collected: 7.6×10^9/l, range 2.8-37.6 10^9/l). In all cases, molecular evaluation of the apheresis product was negative for the *PML–RARa* gene. Negativity was also confirmed on bone marrow before ASCT in all patients, so that they were autografted with a molecularly negative graft in MR.

The conditioning regimen consisted of oral busulphan plus cyclophosphamide (BuCY) in 4 patients, BAVC (carmustine, amsacrine, etoposide and ARA-C) in 2 patients (28), oral Bu plus continuous infusion high-dose idarubicin in 4 patients (29) and intravenous busulphan plus high-dose idarubicin (30) in 2 patients.

The median number of CD34$^+$ cells infused was 7.4×10^9/l. No acute toxicity was recorded after PBSC infusion. The median time to granulocyte recovery to $>0.5\times10^9$/l and platelet recovery to $>20\times10^9$/l was 12 (range 9-20) and 17 (range 9-46) days, respectively. All febrile patients received empiric broad-spectrum antibiotic therapy, while liposomal amphotericin B was administered to four patients as empiric treatment. Overall, 11 patients developed fever; in detail, there were 10 episodes of fever of unknown origin (FUO) and one bacterial sepsis; in all cases fever disappeared at the time of neutrophil recovery after broad-spectrum antibiotic therapy. No episode of grade 2 or higher extra-hematological toxicity was observed, apart from oral mucositis, which occurred in 6 patients (46%) and needed total parenteral nutrition in all cases. In all patients red cell concentrates were given to maintain the Hb level >8 g/dl, while platelet concentrates were administered to keep a platelet value $>10\times10^9$/l. All transfused blood products were depleted of leukocytes to minimize the risk of transfusional graft *versus* host disease. The median number of packed red blood cell units and platelet units were 3 (1-4) and 2 (0-6), respectively. No maintenance or consolidation therapy after ASCT was given to any patient.

After a median follow-up of 40 months from diagnosis and 25 months from ASCT, 11 patients are alive; 10 of them are in sustained MR; one patient relapsed after ASCT, achieved a third molecular CR and is on a waiting list for allogeneic SCT from an unrelated donor. Two patients relapsed and died in the setting of progressive disease. Overall survival of the whole patient population is shown in Figure 1, and DFS from the time of ASCT is shown in Figure 2. The therapeutic results, hematopoietic recovery and supportive treatment are summarized in Table I.

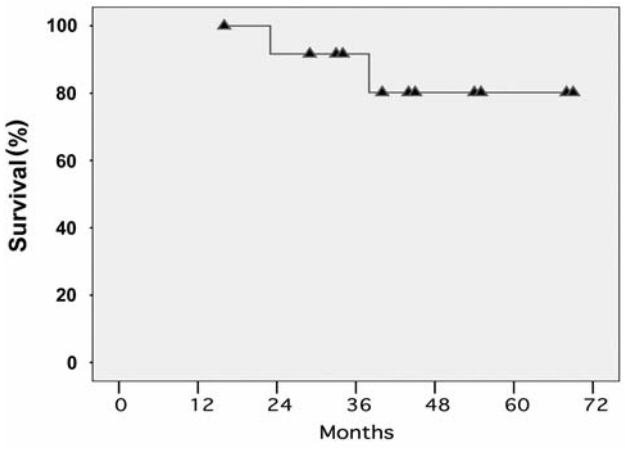

Figure 1. *Overall survival for the whole patient population.*

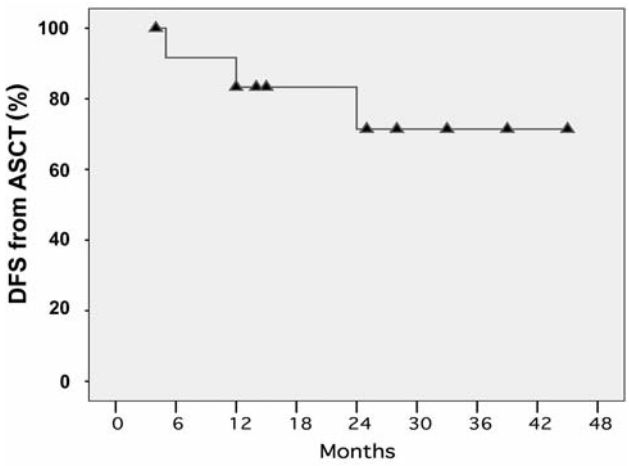

Figure 2. *Disease-free survival (DFS) from the time of autologous stem cell trasplantation (ASCT).*

Table I. *Therapeutic results and toxicity.*

	n
Conditioning regimen	
BuCy	4
BAVC	2
IBu	7
Neutrophils >0.5×10^9/l, days (range)	12 (9-20)
Platelets >20×10^9/l , days (range)	17 (9-46)
FUO	10
Documented infections	1
Oral mucositis	6
TRM	0
Alive/dead	11/13
Alive in MR	10
Median OS	Not reached
Median DFS from ASCT	Not reached

BuCy: Busulphan,cyclophosphamide; BAVC: carmustine, amsacrine, etoposide, cyclophoshamide; IBu: idarubicin, busulphan; TRM: transplant-related mortality; MR: molecular remission; OS: overall survival; DFS: disease-free survival; ASCT: autologous stem cell transplantation.

Discussion

The role of SCT in APL is still matter of debate (13). However, there is general consensus that ASCT and allogeneic-SCT have no role in patients in first molecular CR (3). On the contrary, the optimal algorithm for managing patients with relapsed APL who achieve a second remission after administration of an ATO-based or alternative salvage regimens has not yet been established (31-33). Previous studies have clearly shown that long-term survival can be achieved with either autologous or allogeneic SCT, but morbidity and mortality remain substantially higher in patients receiving allogeneic-SCT. In a previous study, we demonstrated the possibility of mobilizing and collecting *PML-RARa*-negative PBSCs after consolidation therapy in relapsed APL patients (14). Other authors confirmed our findings, clearly showing that ASCT performed during molecular remission is a treatment option for pediatric patients with relapsed APL and may provide durable leukemia-free survival without the complications of allogeneic transplantation (34). More recently, mobilization of *PML–RARa*-negative PBSCs has been achieved with a combination of G-CSF and CXCR4 blockade in a relapsed APL patient pretreated with arsenic trioxide and failing to mobilize after consolidation chemotherapy (35). In the present study, we autografted a series of 13 APL patients who had relapsed after an ATRA/chemo-based regimen. In all patients, molecularly negative PBSCs were collected and reinfused after conditioning with different regimens in patients in second molecular CR. Only 3 patients relapsed after ASCT and neither median DFS nor median OS have been reached after a median follow-up of 45 months from diagnosis for surviving patients (Figures 1 and 2), suggesting a substantial chance of cure. In addition, no case of TRM occurred and non-hematological toxicity was mild, with the exception of severe oral mucositis occurring in patients conditioned with high-dose idarubicin and busulphan. In addition, in more than half of patients, the duration of second MR is longer than 24 months and in 7 of them (56%) longer than the first MR. In this series, most patients had a first CR lasting for more than one year and this may have accounted for the favorable results, given the pivotal prognostic role of the duration of the first CR in non M3 AML (36) as well as in APL (37). Furthermore, given that in all patients were in MR, we may have autografted potentially cured patients. However, while there is suggestion for long-term survival for a minority

of relapsed APL patients reinduced and then treated with ATO/ATRA–based maintenance regimens, consolidation with ASCT has recently reported as being associated with a significantly superior clinical outcome (23).

A potential limitation of our study lies in the relatively low number of patients analyzed in a retrospective manner at two hematological institutions. In addition, salvage treatment as well as conditioning regimens differed among patients. Notwithstanding, the final aim of salvage therapy, *i.e.* second MR, was reached in all patients and, in all cases, PBSCs were negative for the *PML–RARa* gene. Therefore, our series can be considered homogeneous, in that all patients were autografted in MR with molecularly negative graft. Furthermore, it should be considered that a prospective randomized trial aimed at comparison between ASCT- and allogeneic-SCT in patients with APL in second MR is clearly infeasible, given the low number of patients who would be eligible for the trial in contrast to the high number needed to reach statistical significance. In conclusion, these results suggest that ASCT performed with a molecularly negative graft in APL patients in second MR offers a valid chance for achieving a cure. Such an approach should be considered even in relapsed patients with an HLA-compatible donor, namely in those with a first CR lasting more than one year or in elderly individuals.

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