Acute Myeloid Leukemia

Prolonged molecular remission after autologous stem cell transplantation in relapsed acute promyelocytic leukemia

Six patients with relapsed acute promyelocytic leukemia (APL) received autologous stem cell transplantation (ASCT) in second (n=5) or fourth (n=1) molecular remission with a molecularly negative graft. After a median follow-up of 33 months from ASCT, 5 patients are alive in molecular remission and one died 27 months after autograft from refractory relapse.

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Despite considerable progress in the management of APL,[1] relapse still occurs in approximately 20% of cases and, after achievement of second complete remission (CR), the optimal strategy is still controversial.[2] Encouraging results have been reported in relapsed APL patients autografted in second molecular remission, independently of the positivity of the graft for the PML/RARα gene.[3-4] We describe the treatment results from a series of 6 patients autografted in second (n=5) or fourth (n=1) molecular remission by a molecular negative apheresis product or bone marrow harvest. The patients' main characteristics are summarized in Table 1. Five patients did not have an HLA identical donor, while the patient autografted in fourth remission had relapsed after an allogeneic stem cell transplant (alloSCT). All patients (3 with classical APL, 3 with variant APL) were positive for either the translocation t(15;17) or PML/RARα fusion gene (4 bcr1 and 2 bcr3). Details on molecular studies have been provided elsewhere.[5] Five patients were considered at high risk and one at intermediate risk, according to the Sanz score.[6] At diagnosis, five patients had received the GIMEMA/AIDA protocol,[7] one had received daunorubicin plus cytarabine (ARA-C). At the end of consolidation, performed according to the GIMEMA/AIDA protocol, all patients had achieved molecular remission. Relapse was hematologic in 5 cases, molecular in 1. Salvage therapy consisted of all-trans retinoic acid (ATRA) in 2 patients, intermediate dose ARA-C (IDARA-C) plus mitoxantrone (Mito) in 1, arsenic trioxide (ATO) in 2, and ATRA + ATO in the patient who relapsed after alloSCT. After consolidation with IDARA-C + Mito, all patients achieved molecular remission and all received a further identical course as mobilizing therapy. In 5 patients a median of 5.06×10^6 CD34$^+$ cells/kg (range 2.7-10) was collected after a median of 2 aphereses (range 2-3); in one patient who failed to mobilize cells into the periphery, hematopoietic stem cells were obtained by bone marrow harvest (CFU-GM: 16×10^4/kg). In all cases, molecular evaluation of the apheresis product or bone marrow harvest was negative for the PML/RARα gene. The diagnosis of molecular remission or relapse was based on two consecutive evaluations at a one month interval.

In 4 patients the conditioning regimen consisted of continuous infusion of high dose idarubicin plus oral busulphan,[8] while 2 patients received the BAVC regimen.[9] 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 days (range 9-46), respectively. There were 4 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-hematologic toxicity was observed. No maintenance or consolidation therapy after ASCT was given to any patient. After a median follow-up of 57 months from diagnosis and 33 from ASCT, five patients are alive 10, 31, 36, 37 and 68 months after ASCT and all of them are in sustained molecular remission. One patient relapsed 12 months after ASCT and died from refractory disease 15 months later. The therapeutic results, hematopoietic recovery and supportive treatment are summarized in Table 2.

This study is unique in that a PML/RARα negative stem

Table 1. Characteristics of the patients.

	Sex	Age (at diagnosis)	FAB	PML/RARα	Induction	CR1 duration (months)	Relapse	Salvage	Relapse→ASCT (months)	Age (at ASCT)
#1	F	38	M3v	bcr3	AIDA	15	Hem	ATO	5	39
#2	M	23	M3	bcr1	AIDA	12	Mol	ARA-C+Mito	4	25
#3	M	35	M3v	bcr1	AIDA	17	Hem	ATRA	5	37
#4	F	14	M3	bcr1	Dauno+ARA-C	20	Hem	ATRA	4	16
#5	M	43	M3v	bcr3	AIDA	11*	Hem	ATO+ATRA*	4	47
#6	M	66	M3	bcr1	AIDA	14	Hem	ATO	4	69

**CR1 duration: 17 months; CR2 obtained with ARA-C+ Mito and consolidated with alloSCT; CR2 duration: 15 months; CR3 obtained with ATO and consolidated with gentuzumab-ozogamycin.*

Table 2. Therapeutic results and hematopoietic recovery.

	Conditioning regimen	Neut>0.5×10^9/L (days)	Plt>20×10^9/L (days)	RBC units	Platelet units	OS from diagnosis (months)	2nd molecular remission duration (months)	Follow up from ASCT (months)
#1	IBu	9	9	1	1	58+	38	36+
#2	IBu	13	14	2	2	49+	34	31+
#3	BAVC	20	46	5	9	50	12	27
#4	BAVC	13	16	2	3	93+	69	68+
#5	IBu	11	13	2	3	59+	12*	10+
#6	IBu	10	19	0	3	57+	40	37+

**4th molecular remission.*

cell inoculum was used in APL patients in second (n=5) or fourth (n=1) molecular remission. In this series all 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 acute myeloid leukemia.[10] No transplant-related deaths occurred and extra-hematologic toxicity was mild. Five out of 6 patients (83%), including one who relapsed after alloSCT, are alive with no evidence of molecular disease after a median follow-up of 33 months from ASCT and 57 from diagnosis. Of note, in four out of five cases, the duration of second molecular remission is longer than two years and a sustained molecular remission has also been achieved in the patient who relapsed after alloSCT. These results suggest that ASCT performed with a molecularly negative graft in APL patients in second molecular remission offers a valid chance for achieving cure. Such an approach should be also considered in relapsed patients with an HLA compatible donor, namely in those with a first CR lasting more than one year or in elderly individuals.

Felicetto Ferrara, Salvatore Palmieri,*, Mario Annunziata,* Barbara Pocali,* Assunta Viola,* Fabrizio Pane°*

**Division of Hematology and Stem cell Transplantation Unit, Cardarelli Hospital, Naples; °CEINGE Biotecnologie Avanzate, Department of Biochemistry and Medical Biotechnology, Federico II University, Naples, Italy*

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Correspondence: Felicetto Ferrara, via Nicolò Piccinni 6, 80128 Naples, Italy. Phone: international +39.081.7472241. Fax: international +39.081.7472241. E-mail: felicettoferrara@katamail.com

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Acute Leukemia

Analysis of fatal intracranial hemorrhage in 792 acute leukemia patients

Forty-one of 792 acute leukemia patients suffered fatal intracranial hemorrhage (FICH). Acute promyelocytic leukemia was the most common subtype. Achievement of complete remission in AML was significantly influenced by FICH. FICH accounts for about half of deaths from hemorrhage and this proportion has not changed despite improvements in leukemia management.

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Hemorrhagic complications are common in patients with acute leukemia, constituting the second most frequent cause of death in such patients.[1,2] Intracranial hemorrhage (ICH) is the most common hemorrhagic complication in acute promyelocytic leukemia (APL)[3] and is also associated with other acute leukemias such as acute monocytic leukemia and acute lymphoblastic leukemia.[4-8] We examined the features of hemorrhage and ICH in 792 patients with acute leukemia diagnosed between July 1998 and March 2003. Fatal ICH (FICH) was defined as an ICH which was a leading cause of death. Early FICH (group 1) was defined strictly as an event that occurred within seven days of diagnosis of acute leukemia and included cases that presented with FICH. FICH which occurred more than seven days after diagnosis was defined as late FICH (group 2). In all cases, radiological imaging studies such as computed tomography or magnetic resonance imaging were required for confirmation of ICH. The median follow-up was 45.6 months, and 67 (8.5%) patients were lost to follow-up. By the reference date, 419 (52.9%) patients had died. The cause of deaths was hemorrhage in 79 (18.9%) of these patients. At the time of diagnosis, 158 (19.9%) patients presented with various hemorrhagic problems such as epistaxis and petechiae.

Analyzable FICH occurred in 41 (51.9%) of the 79 patients who died from hemorrhage. There were 6 non-fatal symptomatic cases of ICH. Twenty-seven of the FICH were early and 14 were in group 2. At presentation, 13 patients already had signs of ICH which was then fatal. ICH significantly shortened the probability of overall survival in acute leukemia patients. The most common subtype of leukemia in which FICH occurred was APL (n = 18, 43.9%). DIC was the most common probable cause of FICH in all patients and in group 1 patients (n = 17, 41.5%; n = 16, 39.0%, respectively). The patients' status at FICH were: CR in two patients (4.9%), relapse in six (14.6%), and post-SCT relapse in two (4.9%). Patients in group 1 showed a more prolonged PT ($p < 0.001$) and lower serum fibrinogen levels ($p = 0.032$) than did those in group 2. While the time from diagnosis to hemorrhage was longer in group