

Autologous bone marrow transplantation for patients with acute myeloid leukaemia: prospective follow-up study

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Objective. To study the use of autologous bone marrow transplantation to treat acute myeloid leukaemia when complete remission had been achieved and when no human leukocyte antigen–matched related donor was available.

Design. Prospective follow-up study.

Setting. Government hospital, Hong Kong.

Patients. Eight patients (median age, 34 years [range, 16-45 years]) with acute myeloid leukaemia in whom complete remission had been achieved.

Intervention. Conditioning regimen of carmustine, amsacrine, etoposide VP-16, cytarabine, and infusion of unpurged marrow.

Main outcome measures. Median time taken to reach neutrophil and platelet counts of $\geq 0.5 \times 10^9/L$ and $\geq 20 \times 10^9/L$, respectively; mortality and relapse rates; and follow-up regimens used.

Results. Engraftment was successfully achieved in all patients and there were no early procedure–related mortalities. The median times required to reach a neutrophil count of $\geq 0.5 \times 10^9/L$ and a platelet count of $\geq 20 \times 10^9/L$ were 30 days (range, 18-36 days) and 38 days (range, 15-53 days), respectively. The median duration of hospital stay was 37 days (range, 25-43 days). Two patients died of a relapse of leukaemia at 6 and 9 months post-transplantation. Two patients experienced relapses: one at 8 months post-transplantation, for which conventional chemotherapy was restarted, and one at 18 months; treatment with all-trans-retinoic acid and conventional chemotherapy achieved a third complete remission in the latter patient, who had acute promyelocytic leukaemia. Continuous remission has been achieved in four of the eight patients after a median follow-up duration of 26 months (range, 6-43 months).

Conclusion. Autologous bone marrow transplantation is an acceptable treatment for patients with acute myeloid leukaemia who lack a human leukocyte antigen–matched related donor.

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Key words: Antineoplastic agents, combined; Bone marrow transplantation; Combined modality therapy; Leukemia, myelocytic, acute; Survival analysis

Introduction

In the past 30 years, the treatment of acute myeloid leukaemia (AML) has evolved and improved considerably. The general trend in the therapeutic strategy has been to administer aggressive treatment

early, and as soon as the first complete remission has been achieved. The rationale has been to provide maximum antileukaemic effect by giving consolidation chemotherapy (or intensification) at a stage of minimal residual disease, in an effort to eradicate the remaining leukaemic cells in the patient's body. Whereas completely eradicating leukaemia may not be possible, indirect evidence has shown that curing patients of the disease is achievable if the tumour burden can be reduced to a level low enough to be controlled by the patient's own immune system.¹ Such a level can be obtained, although still unpredictably, by modern conventional chemotherapy alone or by high-dose myeloablative regimens, with or without the use of total-body irradiation followed by

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stem cell transplantation. Pooled results from single-centre and large randomised controlled studies indicate a 3-year disease-free survival rate of between 40% and 60%, and a relapse rate of between 31% and 50% for patients in whom autologous bone marrow transplantation (BMT) was performed when the first complete remission (CR1) had been achieved.¹

Whether autografting should be performed during CR1 or whether it should be used as salvage treatment after the second complete remission (CR2) remains a controversial issue. Autologous BMT is however a well-accepted method of consolidating AML during CR2. The use of the pretransplantation BAVC conditioning regimen of carmustine (1,3-bis-[2-chloroethyl]-1-nitrosourea [BCNU]), amsacrine, etoposide VP-16, and cytarabine has a transplantation-related mortality of only 5%, and a long-term disease-free survival rate of 42% for patients with AML who receive an autograft during CR2.²⁻⁴ We report on eight patients with AML in CR1 or CR2 who were treated with high-dose chemotherapy followed by the reinfusion of unpurged cryopreserved autologous bone marrow.

Methods

Patient selection

Between June 1995 and December 1998, 23 patients had received autografts for various haematological malignancies and solid tumours at the Queen Elizabeth Hospital. Eight consecutive patients with AML in CR1 or CR2 without a human leukocyte antigen-matched related donor were considered as suitable candidates to receive a regimen of aggressive chemotherapy. Their eligibility for recruitment into the autologous BMT programme using the BAVC conditioning regimen required the absence of myelodysplastic features of the bone marrow, adequate renal and hepatic function, no uncontrolled infection, a normal cardiac ejection fraction (left ventricular ejection fraction >50%), and signed informed consent.

Bone marrow preparation

Bone marrow was harvested while the patients received general anaesthesia during CR1 (n=4) or CR2 (n=4). The marrow collected from bilateral posterior iliac crests was processed by using a cell separator (CS 3000 plus; Baxter, Unterschleissheim, Germany) to concentrate the mononuclear cells and to reduce their volume to facilitate storage. The marrow was cryopreserved with 10% dimethyl sulphoxide by using a programmed freezer and stored at -190°C in liquid nitrogen. The median interval from harvest to the autologous BMT was 6 weeks (range, 2-30 weeks). The median number of mononuclear marrow cells and granulocyte-macrophage colony-forming cells that were collected was 0.98×10^8 /kg body weight (range, 0.37 - 2.53×10^8 /kg) and 4.29×10^4 /kg (range, 2.83 - 19.70×10^4 /kg), respectively (Table 1).

Conditioning regimen

Intrathecal methotrexate 10 mg/m^2 was given in four doses during 2 weeks before the conditioning chemotherapy, as central nervous system prophylaxis. All patients received the four-drug BAVC schedule (BCNU 800 mg/m^2 on day -6; amsacrine 150 mg/m^2 on days -5, -4, and -3; VP-16 150 mg/m^2 on days -5, -4, and -3; and continuous infusion of cytarabine 300 mg/m^2 on days -5, -4 and -3). Bone marrow was reinfused on day 0, after the patients had rested for 2 days.

Ciprofloxacin 500 mg twice daily and fluconazole 100 mg twice daily were given as antibacterial and antifungal prophylactic treatments, respectively. Acyclovir 400 mg twice daily was given to prevent herpes virus infection, whereas inhalation pentamidine 300 mg was as prophylaxis against *Pneumocystis carinii* pneumonia. Broad-spectrum antibiotic therapy was commenced if fever ($>38^\circ\text{C}$) developed when the neutrophil count was less than 0.5×10^9 /L. Patients in whom fever persisted for 72 to 96 hours after the initiation of antibiotic treatment and patients with documented fungal infections received intravenous

Table 1. Details of haematopoietic recovery

Patient	Mononuclear marrow cells ($\times 10^8$ /kg)	CFU-GM* ($\times 10^4$ /kg)	Time taken to reach counts of:	
			Neutrophils $\geq 0.5 \times 10^9$ /L (days)	Platelets $\geq 20 \times 10^9$ /L (days)
1	1.16	19.70	32	33
2	2.53	3.09	27	53
3	2.27	4.38	26	53
4	1.38	3.59	18	15
5	0.37	2.83	36	36
6	0.52	4.20	36	45
7	0.48	4.56	29	40
8	0.79	10.70	31	31
Median	0.98	4.29	30	38

* CFU-GM Granulocyte-macrophage colony-forming cells

Table 2. Patient characteristics

Patient No.	Sex/age (years)	FAB* classification	Duration of CR1 [†]	Status at ABMT [‡]	Follow-up [§] (months)	Treatment outcome
1	F/31	M3	14	CR2	9	Relapsed and died post-ABMT
2	M/36	M4	2	CR2	43	CR2
3	M/32	M4	38	CR2	40	CR2
4	M/41	M3	25	CR2	39	Relapsed 18 months post-ABMT; achieved CR3 since Dec 1997
5	M/16	M4	-	CR1	13	CR1
6	F/45	M5b	-	CR1	6	Relapsed and died post-ABMT
7	M/29	M2	9	CR2	8	Relapsed 8 months post-ABMT
8	M/44	M4	-	CR1	6	CR1

* FAB French-American-British

† CR1 first complete remission

‡ ABMT autologous bone marrow transplantation

§ Duration from date of reinfusion to 31 March 1999 or to date of death

|| CR2 second complete remission

||| CR3 third complete remission

amphotericin B. A 28-day course of oral cyclosporin A 100 mg twice daily was commenced on the day of the bone marrow reinfusion in an attempt to induce autologous cutaneous graft-versus-host disease.^{5,6} All blood products were irradiated with 20 Gy of gamma radiation before their transfusion to prevent transfusion-related graft-versus-host-reaction.

Results

Patient characteristics

The characteristics of the eight patients are shown in Table 2. The median age was 34 years (range, 16-45 years) and the median duration of CR1 was 14 months (range, 2-38 months). The autologous BMT procedure was performed after a median interval of 5 months (range, 4-9 months) from the start of CR1 (n=3) and 7 months (range, 3-10 months) from the start of CR2 (n=5).

Toxicity of treatment

The BAVC regimen was well tolerated, and nausea and vomiting were the only major side effects. No patient developed grade 3 mucositis or required parenteral nutrition and no episodes of severe haemorrhage were observed. All patients experienced fever during the neutropenic phase; cultures from five of the eight patients were positive for bacteria (three were Gram positive and two were Gram negative). There were no documented cases of fungal infection, but intravenous amphotericin B was required empirically in three patients. One patient developed cytarabine-related neurotoxicity—that is, marked irritability and involuntary movements of all four limbs; these symptoms subsided 10 days after the conditioning chemotherapy. There were no deaths during the first 100 post-transplantation days.

Effects of engraftment and follow-up

The patient characteristics and details of haematopoietic recovery are shown in Tables 1 and 2, respectively. The

median time required to attain an absolute neutrophil count higher than 0.5×10^9 /L was 30 days (range, 18-36 days). A platelet count higher than 20×10^9 /L was observed after a median of 38 days (range, 15-53 days). Two patients required more than 50 days to achieve a platelet count of 20×10^9 /L. No correlation was observed between the number of nucleated bone marrow cells or granulocyte-macrophage colony-forming cells reinfused and the rate of haematological recovery. The median hospital stay was 37 days (range, 25-43 days).

As at 31 March 1999, four patients were in continuous complete remission after autologous BMT: two received transplantation during CR2 and two during CR1. Four patients experienced relapse after a median time of 8.5 months (range, 6-18 months). Two of the four patients died soon after relapse, and the third patient relapsed at 8 months post-transplantation, for which conventional chemotherapy was restarted. The fourth patient, in whom acute promyelocytic leukaemia (APL) relapsed 18 months post-transplantation, achieved a third complete remission at 22 months after being given all-trans-retinoic acid (ATRA) and conventional chemotherapy; the patient is currently still in complete remission. No definite cutaneous graft-versus-host reaction was observed in any of the patients.

Discussion

The role of autologous bone marrow transplantation for acute myeloid leukaemia

The results of eight recent prospective randomised studies⁷⁻¹⁴ are summarised in Table 3. Some of the studies have consisted of two treatment arms—namely, allogeneic and autologous BMT,^{8,11,13} or autologous BMT and conventional chemotherapy.^{12,14} The three-armed studies have compared all three treatment modalities.^{7,9,10} In all these studies, the marrow used for autologous BMT was unpurged and in most of

Table 3. Prospective randomised controlled studies comparing transplantation with conventional chemotherapy

Study	No. of patients (age [years])	No. of patients treated*	Relapse frequency (%)			LFS [†] rate (intention-to-treat) [%]			Treatment favoured
			Allo-BMT [‡]	Auto-BMT [§]	Chemo	Allo-BMT	Auto-BMT	Chemo	
Reiffers et al ^{7¶}	204 (<45)	39/50	24	56	58	67	42	42	Allo-BMT
Lowenberg et al ⁸	117 (<60)	32/50	34	60	-	51	35	-	Allo-BMT
Harousseau et al ⁹	535 (<50)	75/114	37	45	55	44	44	40	None
Zittoun et al ¹⁰	941 (<45)	95/128	24	41	57	55	48	30	Allo- and auto-BMT
Mitus et al ¹¹	94 (<60)	27/53	20	50	-	56	45	-	Neither
Ravindranath et al ¹²	649 (<15)	115/219	-	31	58	-	38	36	Neither
Sierra et al ¹³	159 (<51)	47/68	23	37	-	31	50	-	Auto-BMT
Burnett et al ¹⁴	1966 (<56)	125/190	-	37	58	-	54	40	Auto-BMT

* Expressed as No. of patients receiving autografts/No. of patients randomly assigned to receive autografts

[†] LFS leukaemia-free survival

[‡] Allo-BMT allogeneic bone marrow transplantation

[§] Auto-BMT autologous bone marrow transplantation

^{||} Chemo chemotherapy

** This study compared allo-BMT (group 1) with intensive consolidation (with or without auto-BMT) (group 2); treatment outcome was evaluated by whether complete remission was achieved and not by intention-to-treat analysis

the studies, statistical analysis consisted of intention-to-treat analysis. The studies that compared allogeneic and autologous BMT found more favourable results for the former transplantation modality.^{8,11,13} But the studies that compared autologous BMT with conventional chemotherapy found a significantly reduced frequency of relapse and better leukaemia-free survival rate for the recipients of autologous BMT.^{12,14} A recent meta-analysis of seven randomised trials conducted between 1984 and 1995,¹⁵ however, has shown that transplant-related mortality and toxicity limit the usefulness of autologous BMT. The use of high-dose cytarabine, as tested by the Cancer and Leukemia Group B study,¹⁶ may lead to a treatment outcome comparable to that of autologous BMT.

Preparative regimen for autologous bone marrow transplantation

Before BMT is performed, a preparative regimen of chemotherapy with or without radiotherapy is given. For patients undergoing allogeneic BMT, the preparative regimen has the following objectives: cyto-reduction and eradication of any residual leukaemic cells; immunosuppression to abrogate the immunological resistance to engraftment; and (if possible) the creation of space within the micro-environment to allow engraftment of the donor stem cells. The immune-mediated graft-versus-leukaemia effect conferred by the allogeneic transplant adds to the antileukaemic effect and is an important component of relapse prevention. For autologous BMT, immunosuppression is not required and the preparative regimen is used to provide maximal-dose intensive therapy, with a goal of eradicating any remaining leukaemic cells. This method has no allogeneic graft-versus-leukaemia effect, and leukaemic cells that contaminate the stored autologous bone marrow may contribute to relapse.

Maximally tolerated doses of chemotherapy are used; however, the doses are limited by non-haematopoietic toxicity.

Two pretransplantation regimens are commonly used in autologous BMT: cyclophosphamide (CY) 120 mg/kg with total-body irradiation (TBI)¹⁷ and busulfan-CY combination therapy. In the latter treatment, busulfan 16 mg/kg is given over 4 days, followed by either CY 200 mg/kg over the next 4 days,¹⁸ or CY 120 mg/kg over the next 2 days,¹⁹ to reduce drug toxicity. High-dose etoposide (VP-16) 60 mg/kg has been recently introduced as combination therapy with TBI²⁰ or busulfan.^{21,22} A third pretreatment regimen is the BAVC regimen (BCNU 800 mg/m², amsacrine 450 mg/m², etoposide VP-16 450 mg/m², and cytarabine 900 mg/m²). Because of its reduced toxicity, the BAVC regimen is particularly suitable for older patients and/or patients in CR2.²⁻⁴ Studies of autologous BMT have generally used the same regimens that were developed for use in allogeneic BMT. The immunosuppressive effects that are needed for allogeneic BMT, however, are not necessary or desirable for autologous BMT. In addition, autologous transplant recipients may be capable of tolerating more intensive regimens, because graft-versus-host disease is unlikely to develop; these patients also recover their immune constitution more rapidly than do allogeneic transplant recipients, thereby lowering their risk of infection by, for example, cytomegalovirus.

The toxicity of the conditioning regimen used for recipients of autologous BMT is an important issue in evaluating the eligibility of autografting after achieving CR1. Until now, no studies have established the superiority of any particular high-dose regimen.²³ The BAVC regimen was used as the conditioning

regimen in this study, because the usual busulfan/CY or CY/TBI regimens might not have been optimal for this group of patients: both treatments have a relatively high transplant-related toxicity, especially liver veno-occlusive disease.²⁴

Role of purging in autologous bone marrow transplantation

Relapse due to either residual host disease or the reinfusion of leukaemic cells remains the principal cause of treatment failure after autologous stem cell transplantation. Although it is intuitively attractive to remove putative leukaemic cells from autografts prior to transplantation, there are limited data suggesting that purging autografts has any favourable effect on relapse or disease-free survival rates.²⁵ Most of the purging techniques described have adverse effects such as delayed haematopoietic or T-cell reconstitution. There is a need for large, well-designed trials that specifically address the value of a particular purging technique on relapse and disease-free survival rates after autologous stem cell transplantation.²⁵ In many of the prospective randomised controlled studies, the marrow used for autologous BMT was unpurged. Considering the cost-effectiveness of the current purging techniques, unpurged marrow in this study was harvested after at least two courses of consolidation chemotherapy to provide stem cell support for the patients.

Use of autologous bone marrow transplantation for acute promyelocytic leukaemia

Data collected before the introduction of ATRA have indicated that recipients of autografts for APL can achieve a 7-year leukaemia-free survival rate of 48% for patients in CR1 and 31% for those in CR2.²⁶ Results achieved by allogeneic BMT were not superior because of a very high transplant-related mortality rate of 42%, compared with a rate of 18% following autologous BMT.²⁶ The management of APL has changed since 1990, with the advent of ATRA and its use in combination with chemotherapy to induce remission. Other advancements include the detection of PML/RAR- α fusion transcripts by polymerase chain reaction (PCR) analysis and the demonstration of its prognostic relevance to detect minimal residual disease, as well as the design of better treatment strategies. In a recent trial, induction with ATRA and idarubicin followed by three consolidation courses resulted in 95% remission and a 2-year leukaemia-free survival rate of approximately 80%.²⁷ At the end of the consolidation period, 98% of the patients had undetectable levels of PML/RAR- α transcripts.²⁷ Hence, stem cell transplantation cannot be recommended as part of the front-line therapy of APL.

In contrast, in the few cases of relapse, the use of ATRA, arsenic compounds, and chemotherapy can result in CR2, and autologous BMT should be seriously considered. It has been proposed that patients in CR2 who remain PCR-positive for the PML/RAR- α fusion transcripts should proceed to allogeneic BMT if possible, whereas PCR-negative patients could be given autologous BMT if a longer disease-free survival time is expected.²⁸ In this study, two patients with APL in CR2 received autografts, but they relapsed 9 and 18 months post-transplantation. Analysis using PCR was not performed before the autologous BMT to detect PML/RAR transcripts. One patient died soon after relapse; the other patient achieved a third complete remission by using ATRA and conventional chemotherapy, and is currently still in complete remission. The two relapses in this study might be related to the presence of resistant leukaemic cells or the non-optimal use of the BAVC preparative regimen in this group of patients.

Conclusion

Our data show that the BAVC regimen has good anti-leukaemic activity and is associated with modest and acceptable acute and long-term toxicity. When used as conditioning regimen with unpurged marrow for autografting patients with AML in CR2, the BAVC regimen is superior to conventional chemotherapy.²⁻⁴ Whether its use as conditioning chemotherapy for patients with AML in CR1 is recommended is yet to be determined and longer follow-up is required. Prospective randomised controlled trials that compare different preparative chemotherapy regimens, including BAVC, are required to answer this question.

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