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ORIGINAL ARTICLE

Myelodysplastic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma

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Long-term survivors after autologous peripheral blood stem cell transplantation (APBSCT) for lymphoma or Hodgkin's disease are known to have a high risk of developing myelodysplastic syndrome (MDS), but the risk of MDS is not clear for patients transplanted for myeloma. We reviewed the outcomes for 82 myeloma patients who underwent APBSCT at our center. The group included 47 men and 35 women of median age 56 years (range: 37–74 years). Median time from diagnosis to APBSCT was 8.2 months (range: 2.6–86.1 months). Before coming to transplantation, 28% had received oral melphalan (MEL), 98% received other chemotherapy and 34% received radiation. A single APBSCT was provided for 68, and 32% underwent APBSCT more than once. High-dose MEL alone was used as the preparative regimen for 83%, and the remainder received at least one APBSCT with a more intensive preparative regimen. Ten patients (12%) developed MDS. The 5-year cumulative incidence is 18% (95% confidence interval, 9–30%). There were no demographic factors associated with an increased risk of developing MDS. Median survival after the diagnosis of MDS was 18 months. There is a relatively high risk of MDS after APBSCT for myeloma, and optimal therapy has not been established for these patients.
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Introduction

Autologous peripheral blood stem cell transplantation (APBSCT) has been shown to have a significant impact on overall and/or event-free survival for patients with myeloma.[1–5] While relapse remains the most common cause of treatment failure for these patients, event-free survival has been extended further with post transplant maintenance therapy,[6,7] and late non-relapse mortality has subsequently become an issue.[8]

Jantunen *et al*.[8] have identified second malignancy, especially therapy-related myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML), as the most frequent cause of late non-relapse mortality after autologous transplantation. For patients transplanted for malignant lymphoma or Hodgkin's disease, the actuarial risk of late MDS or AML varies from 3% to more than 20% at 5-years post transplant.[9] Far less is known about second malignancies after transplantation for myeloma. We have, therefore, evaluated the incidence and outcome of MDS in our myeloma patients.

Patients and methods

Patients

From August 1996 through December 2005, 89 patients with multiple myeloma underwent APBSCT at our center. Six patients died less than 6 months after transplantation, and one patient was lost to follow-up 1 month after transplantation. The records were reviewed for the remaining 82 patients. Data abstracted from the charts included demographic characteristics, induction therapy, mobilization information, cell processing data, transplant preparative regimen, transplant characteristics, maintenance therapy post transplant, response, relapse or progression, treatment after transplantation, development of unexplained abnormalities in the hemogram persisting more than 6 months, results of marrow biopsies before and after transplantation and dates of last follow-up or death. MDS was identified according to the usual criteria.[10] This study was approved by the Methodist Healthcare Institutional Review Board.

Treatment regimens

Stem cells were collected by apheresis following treatment with filgrastim alone (10–12 mcg/kg/day for 5 days) or chemotherapy in addition to filgrastim and/or sargramostim (500 mcg/m^2/day). The chemotherapeutic regimens for mobilization included vincristine 0.4 mg/day i.v. on days 1–4, doxorubicin 9 mg/m^2/day i.v. on days 1–4 and dexamethasone 40 mg/day p.o. on days 1–4 (vincristine, doxorubicin, dexamethasone (VAD)); cyclophosphamide

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750 mg/m^2/day i.v. on days 1–4, doxorubicin 10 mg/m^2/day i.v. on days 1–4 and dexamethasone 40 mg/day p.o. on days 1–4 (cyclophosphamide, doxorubicin, dexamethasone (CAD)); or intermediate dose cyclophosphamide 2–5 g/m^2 i.v. (cyclophosphamide (CYC)) alone. The preparative regimens for transplantation included high-dose melphalan at 140–200 mg/m^2 on day −2 (melphalan (MEL)); carmustine 300 mg/m^2 i.v. on day −7, etoposide 200 mg/m^2/day i.v. on days −6 to −3, cytarabine 400 mg/m^2/day i.v. on days −6 to −3 and melphalan 140 mg/m^2/day i.v. on days −2 (carmustine, etoposide, cytarabine and melphalan (BEAM)), busulfan 1 mg/kg p.o. × six doses on days −4 and −3 and melphalan 100 g/m^2 i.v. on day −2, or busulfan 1 mg/kg p.o. × 12 doses on days −6 to −4 and melphalan 200 g/m^2 i.v. on day −3 (busulfan and melphalan (BU/MEL)), cyclophosphamide 1 g/m^2 i.v. on day −5, mitoxantrone 15 g/m^2 i.v. on days −8 to −6 and thiotepa 250 g/m^2 i.v. on days −8 to −6 (cyclophosphamide, mitoxantrone and thiotepa (CMT)).

Fluorescence in situ *hybridization*

Cryopreserved stem cells stored in ampules were thawed, washed and cultured overnight in Chang's medium (Flow Laboratories, Irwine, UK), and colchicine was added during the last 3 h of incubation. Slides were prepared for karyotyping. Fluorescence *in situ* hybridization (FISH) was performed on interphase nuclei as described previously,[11] using probe 1q25 to assess for der(1:7), ELN (7q11.23) to assess for monosomy 7 and DYZ3 (Yp11.1–q11.1) to assess for loss of the Y chromosome (Vysis, Abbott Molecular Inc., Des Plaines, IL, USA). At least 300 cells were examined for each patient tested.

Statistical considerations

Demographic parameters are reported as the number of patients or the median and range as indicated. Since the blood volumes processed during apheresis varied between patients, the mobilization rate was used to quantify stem cell mobilization. Mobilization rate is defined as (the total number of CD34 cells collected)/(the volume of blood processed in liters during apheresis). The mobilization rate reported is the average of the daily rates for patients with more than one collection. For patients with multiple transplantations, the CD34 cell dose reported refers to the dose used for the last transplantation. Since stem cell collections were usually divided equally, there is a high correlation between first and last CD34 cell dose.

At last follow-up, median time from transplantation for all patients is 30 months (range: 8–114 months). Mann–Whitney *U*-test was used to compare demographic parameters between groups. Prognostic factors for MDS were tested using a Cox proportional hazard model. The rate of developing MDS was calculated as the cumulative incidence with death as a competing risk. Survival was determined as the Kaplan–Meier estimate. The statistical analyses were performed using Stata 8.0 (Stata Corporation, College Station, TX, USA), and the 'stcompet' package was added to calculate cumulative incidence with competing risks.[12] A two-sided P-value < 0.05 was considered significant.

Results

Patients

Characteristics of the 82 evaluable patients are listed in Table 1. The primary induction therapy included VAD for 44% of the patients and MEL alone or in a combination regimen for only 28% of the patients. Radiation was given to 34%. For mobilization, the majority of patients (77%) received CYC alone. For transplantation, high-dose MEL was the most common (91%) preparative regimen for first transplantation. More than one transplantation was performed for 32% of the patients; 18% received high-dose MEL for two transplantations, and 16% had at least one preparative regimen that was more intense than high-dose MEL (Table 1). Maintenance was not provided in a uniform fashion, but 41% of the patients are known to have received some form of maintenance therapy after transplantation, including corticosteroids, thalidomide with or without corticosteroids or interferon. In addition, 57% of the patients have received chemotherapy or radiation for treatment of relapse after transplantation.

MDS after transplantation

Ten patients (12%) have developed MDS (Table 2). These included seven men and three women of median age 61

Table 1 Demographic characteristics

Number of patients	82
Age at APBSCT	56 (37–79) years
Gender	47 men/35 women
Diagnosis to APBCST	8.2 (2.6–86.1) months
Melphalan before APBSCT	23
Treatment before APBSCT	3 (1–5) regimens
Mobilization	
G-CSF	3
VAD	1
CAD	13
CYC	63
Mobilization rate	27.1 (1.8–250.1) × 10^6/l blood processed
Last CD34 dose	5.1 (0.4–35.0) × 10^6/kg
Number of transplants	
1	56
2	22
3	4
Preparative regimen	
MEL	69
BEAM	6
BU/MEL	5
CMT	2
Maintenance	
Yes	41
No	36
Unknown	5
Treated after APBSCT	47

Abbreviations: APBSCT = autologous peripheral blood stem cell transplantation; BEAM = carmustine, etoposide, cytarabine and melphalan; BU/MEL = busulfan and melphalan; CAD = cyclophosphamide, doxorubicin, dexamethasone; CMT = cyclophosphamide, mitoxantrone and thiotepa; CYC = cyclophosphamide; MEL = melphalan; G-CSF = filgrastim; VAD = vincristine, doxorubicin, dexamethasone.

Table 2 Patients with MDS after transplantation

No.	*Age/gender*	*Prior treatment*		*Diagnosis to APBSCT (months)*	*Mobilization rate ($\times 10^6$/l)*	*CD34 dose ($\times 10^6$/kg)*	*Total number of APBSCTs*	*Maximum preparative regimen*	*APBSCT to MDS (months)*	*Survival after APBSCT (months)*
		MEL	*XRT*							
1	48/male	No	No	5.8	21.3	3.80	1	MEL	12.8	25.2 died, MDS and progressive MM
2	62/male	Yes	No	24.1	30.8	5.50	1	MEL	18.1	31.2+alive after non-myeloablative SCT for MDS
3	67/male	Yes	No	71.7	604	2.42	1	MEL	9.6	36.5+alive after non-myeloablative SCT for MDS
4	62/male	No	No	5.5	2.0	1.50	2	CMT	30.4	39.3 died, MDS and sepsis
5	71/male	No	No	7.1	18.1	2.87	1	MEL	26.9	45.0 died after myeloablative SCT for AML
6	67/female	No	No	8.6	17.7	2.90	1	MEL	36.5	49.9+alive with pancytopenia
7	49/female	No	No	5.0	44.5	3.50	3	BEAM	55.5	57.3+alive with pancytopenia
8	60/female	Yes	No	8.3	7.2	2.23	2	MEL	46.1	61.7+alive with pancytopenia
9	57/male	Yes	No	56.3	27.4	5.58	3	BU/MEL	31.4	63.0 died, progressive MM after APBSCT for MDS
10	55/male	Yes	Yes	10.2	2.2	2.00	2	MEL	59.4	64.1 died on treatment for AML
	Median (range)			8.5 (5.0–71.7)	17.9 (2.0–44.5)	2.90 (1.50–5.58)			30.9 (9.6–59.4)	

Abbreviations: AML = acute myelogenous leukemia; APBSCT = autologous peripheral blood stem cell transplantation; BEAM = carmustine, etoposide, cytarabine and melphalan; BU/MEL = busulfan and melphalan; CMT = cyclophosphamide, mitoxantrone and thiotepa; MDS = myelodysplastic syndrome; MEL = melphalan; SCT = allogeneic stem cell transplantation; XRT = external beam radiation to sites of pain or impending fracture.

years (range: 48–71 years) who were transplanted at a median of 8.5 months (range: 5.0–71.7 months) from initial diagnosis of multiple myeloma. Only five of these patients had received MEL alone or in combination for induction. The median mobilization rate during stem cell collection was 17.9×10^6 (range: $2.0–44.5 \times 10^6$) CD34/l blood processed. The median CD34 cell dose was 2.89×10^6 (range: $1.50–5.58 \times 10^6$) CD34/kg. Nine patients had a partial response or better after transplantation, and five patients were treated for relapsed multiple myeloma (MM) after APBSCT.

Cytopenia persisting more than 3 months was the presenting sign of MDS in all patients. Six patients had clonal cytogenetic abnormalities in the marrow to confirm the diagnosis of MDS. The other four patients had morphologic evidence of dysplasia, ineffective hematopoiesis (peripheral pancytopenia with normal or hypercellular marrow), progressive pancytopenia in the absence of myelosuppressive chemotherapy and little or no excess in plasma cells in the marrow.

The cumulative incidence of MDS for all patients was 18% (95% confidence interval (CI), 9–30%) at 5 years (Figure 1). The median time from APBSCT to diagnosis of MDS was 30.9 months (range: 9.6–59.4 months). Since a prolonged course of oral MEL is known to predispose patients to developing MDS, we were interested in knowing the risk in patients treated with a more modern therapy. In our series, 40 patients received VAD or VAD-like induction and underwent one (31 patients) or two (9 patients) transplantations using only high-dose MEL as the preparative regimen; 14 of these also received local radiation pre-induction, and 37 received a single cycle of an alkylator for mobilization. Three of this subset of 40 patients developed MDS for a cumulative incidence of 11% (95% CI, 3–26%).

Factors tested for the multivariate analysis included age (above or below 55 years), gender, use of MEL for induction therapy, number of induction treatments (1–2 vs 3–5 regimens), number of transplantations (1 vs 2–3), maximal intensity of the preparative regimen (MEL vs other), use of maintenance therapy after transplantation, treatment of relapse after transplantation, maximal peripheral blood CD34 count before apheresis (above or below

Figure 1 Cumulative incidence of MDS after APBSCT for myeloma. The cumulative incidence is 18% (95% CI, 9–30%) at 5 years.

Table 3 Cytogenetic studies for patients with MDS after transplantation

No.	*Cytogenetics before APBSCT*	*PBSC FISH*	*Cytogenetics at diagnosis of MDS after APBSCT*
1	ND	ND	20/20 46,XY
2	ND	ND	20/20 46,XY
3	5/20 46,XY, + 1,der(1;7)(q10p10)	5/300 + 1	14/20 46,XY, + 1,der(1;7)(q10:p10)
4	ND	ND	ND
5	21/21 46,XY	0/300 −7	24/30 45,XY,inv(3)(q21;q26),−7
6	20/20 46,XX	0/300 + 1	12/20 46,XX, + 1,der(1;7)(q10:p10)
7	ND	ND	20/20 46,XX
8	ND	3/300 −7	15/20 45,XX,−7
9	13/21 45,X,-Y	0/300-Y	11/14 45,X−Y
10	21/21 46,XY	9/310−7	16/20 43,XY,del(5)(q13),−7,−13,−15,add(19)(p13), + mar

Abbreviations: APBSCT = autologous peripheral blood stem cell transplantation; MDS = myelodysplastic syndrome; ND = not done; PBSC FISH = fluorescence *in situ* hybridization of the cryopreserved peripheral blood stem cells.

the median for the group), mobilization rate (above or below the median for the group) and CD34 cell dose (above or below the median for the group). None of these demographic characteristics were prognostic for development of MDS after APBSCT.

Outcomes

Two of the patients underwent APBSCT for MDS, using stem cells that were collected originally for treatment of myeloma; one had partial recovery of peripheral blood counts but retained the cytogenetic abnormality, and one progressed to AML after the attempted rescue APBSCT. Of the 10 patients with MDS, five patients survived; three had persistent pancytopenia and two had recovery of peripheral blood counts after non-myeloablative allogeneic stem cell transplantation. Five patients have died; one from sepsis while pancytopenic from MDS, two from progressive myeloma with cytopenias from MDS, one during induction for AML and one after myeloablative allogeneic stem cell transplantation for refractory AML. Median survival is 52 months (95% CI, 39–86 months) for all patients transplanted for myeloma, 47 months (95% CI, 33–86 months) for patients who did not develop MDS and 63 months for patients with MDS. The median survival from diagnosis of MDS is 18 months.

Cytogenetic studies

Six of the patients with MDS had clonal cytogenetic abnormalities in the marrow at the time of diagnosis of MDS (Table 3). Marrow biopsy and aspiration for restaging were performed before transplantation in all patients; cytogenetic studies were available for five patients, and two (patients 3 and 9) had the diagnostic clonal abnormality in the marrow before transplantation. Cryopreserved aliquots of stem cells had been tested by FISH for all six patients with clonal cytogenetic abnormalities, and the results were consistent with the diagnostic clonal abnormality in three of them (Table 3, patients 3, 6 and 10).

Discussion

The reported incidence of MDS and/or AML after APBSCT for myeloma has been variable (Table 4). For reports analyzed before 2000, the proportion of patients with MDS or AML was 0–3.7%, and 9–11% for those evaluated later than 2000 (Table 4). In our study, 10 (12%) of 82 patients developed MDS, consistent with the later reports. Two major factors probably account for the increase in the reported rate of this complication. First, the changes in supportive care, new salvage therapies and advances in maintenance therapy have allowed patients to survive longer after APBSCT for myeloma; thus, more patients are at risk. Second, as a result of multiple studies of patients with lymphoma,[9] there is an increased awareness of the possibility of MDS in APBSCT recipients, providing greater impetus for a more complete evaluation of late cytopenias, including marrow cytogenetics, even in patients with known persistent or recurrent myeloma after transplantation. With the potential increasing incidence of MDS after APBSCT for myeloma, it would be of value to understand more about the etiology, prognostic features and appropriate therapy.

Table 4 Reports of MDS or AML after autologous transplantation for myeloma

Reference, year	*No. of patients*	*No. (%)*[a] *of MDS/AML*
Govindarajan *et al.*[13] (1996)	188	7 (3.7)
Sobecks *et al.*[14] (1999)	28	0 (0)
Del Canizo *et al.*[15] (2000)	189	1 (0.5)
Sevilla *et al.*[16] (2002)	22	2 (9.1)
Laurenti *et al.*[17] (2002)	19	2 (10.5)
Current study	82	10 (12.2)

Abbreviations: AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome.
[a]Crude proportion.

In one of the older series from Govindarajan *et al.*,[13] all patients who developed MDS after APBSCT for myeloma had received prolonged (median 24 months) conventional-dose alkylator therapy. These authors, therefore, concluded that prior treatment with MEL was the major cause of MDS in these patients. We found no association between prior treatment with MEL and development of MDS in our patients. In fact, six of our patients with MDS had been transplanted early, within 9 months of diagnosis, without a prolonged course of oral MEL. Further, for the subset of

patients receiving induction with VAD, limited exposure to alkylators for mobilization, and the standard high-dose MEL preparative regimen, MDS was still a problem (cumulative incidence 11%).

That is not to say that prior chemotherapy did not contribute to the MDS. Five of the six patients with clonal cytogenetic abnormalities had a monosomy 7 or der(1:7) abnormalities that have been associated with alkylator-induced MDS. Consequently, even the limited use of an alkylator for mobilization may have had adverse consequences, especially after exposure to doxorubicin for primary induction. Myeloma patients can now be induced successfully without the need for an alkylator or a topoisomerase inhibitor, and PBSC can be collected using growth factor alone for mobilization. Whether this approach will result in a lower incidence of MDS in the transplant recipients remains to be determined.

The preparative regimen, use of maintenance therapy and additional treatment after transplantation were also not associated with the development of MDS in our cohort. However, given the heterogeneity of the population, the number of patients studied may have been too small to detect a significant factor. We did note that most of our patients with MDS fell below the median with regard to mobilization rate and CD34 cell dose, suggesting a pre-existing marrow abnormality. This hypothesis was supported by the rather short time from transplantation to diagnosis of MDS in our patients (median 31 months).

Amigo *et al*.[18] and Abruzzese *et al*.[19] reported detecting cytogenetic clonal abnormalities in peripheral blood progenitor products for patients who developed MDS or AML after autologous transplantation for lymphoma, Hodgkin's disease or solid tumors. In our series, two of five patients tested had clonal cytogenetic abnormalities in the restaging marrow before stem cell collection, and three of six patients' cryopreserved stem cell products had abnormalities consistent with their MDS clones detected by FISH. Consequently, it appears that at least some of our patients had MDS before transplantation. While it would probably be cost prohibitive to test all stem cell products for cytogenetic abnormalities, our data suggest that more extensive testing may be worthwhile in the particularly poor mobilizers.

Treatment of patients with MDS or AML after APBSCT for myeloma is complicated by the extensive prior therapy and advanced age of the patients. Kroger *et al*.[20] suggested that autologous transplantation could benefit these patients, especially if they are young or if a complete remission can be obtained, although the relapse rate remained high (58%). The autologous approach was useful in one of our patients who underwent salvage APBSCT. Myeloablative allogeneic transplantation is associated with a high rate of treatment-related mortality and has generally produced poor outcomes in this setting, with median survivals less than 1 year and long-term survivals less than 20%.[21–24] Two of our patients are surviving after non-myeloablative allogeneic transplantation, which has had less treatment-related mortality in the elderly and heavily pretreated population. While non-myeloablative transplantation has been useful in restoring hematopoietic function in patients with cytopenias due to MDS after transplantation, whether it will effect long-term control of the myeloma remains to be seen.

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References

1 Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF *et al*. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; **335**: 91–97.
2 Barlogie B, Jagannath S, Vesole DH, Naucke S, Cheson B, Mattox S *et al*. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997; **89**: 789–793.
3 Palumbo A, Triolo S, Argentino C, Bringhen S, Dominietto A, Rus C *et al*. Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood* 1999; **94**: 1248–1253.
4 Lenhoff S, Hjorth M, Holmberg E, Turesson I, Westin J, Nielsen JL *et al*. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. *Blood* 2000; **95**: 7–11.
5 Levy V, Katsahian S, Fermand JP, Mary JY, Chevret S. A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. *Medicine* 2005; **84**: 250–260.
6 Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F *et al*. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **354**: 1021–1030.
7 Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L *et al*. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
8 Jantunen E, Itala M, Siitonen T, Koivunen E, Leppa S, Juvonen E *et al*. Late non-relapse mortality among adult autologous stem cell transplant recipients: a nation-wide analysis of 1482 patients transplanted in 1990–2003. *Eur J Haematol* 2006; **77**: 114–119.
9 Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. *Blood* 2000; **95**: 3273–3279.
10 Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR *et al*. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982; **51**: 189–199.
11 Qumsiyeh MB, Tharapel SA. Interphase detection of trisomy 12 in B-cell chronic lymphocytic leukemia by fluorescence hybridization *in situ*. *Leukemia* 1992; **6**: 602–605.
12 Coviello V, Boggess M. Cumulative incidence estimation in the presence of competing risks. *Stata J* 2004; **4**: 103–112.
13 Govindarajan R, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B *et al*. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol* 1996; **95**: 349–353.
14 Sobecks RM, Le Beau MM, Anastasi J, Williams SF. Myelodysplasia and acute leukemia following high-dose chemotherapy and autologous bone marrow or peripheral

blood stem cell transplantation. *Bone Marrow Transplant* 1999; **23**: 1161–1165.
15 Del Canizo M, Amigo M, Hernandez JM, Sanz G, Nunez R, Carreras E *et al*. Incidence and characterization of secondary myelodysplastic syndromes following autologous transplantation. *Haematologica* 2000; **85**: 403–409.
16 Sevilla J, Rodriguez A, Hernandez-Maraver D, de Bustos G, Aguado J, Ojeda E *et al*. Secondary acute myeloid leukemia and myelodysplasia after autologous peripheral blood progenitor cell transplantation. *Ann Hematol* 2002; **81**: 11–15.
17 Laurenti L, Chiusolo P, Garzia MG, Zini G, Sora F, Piccirillo N *et al*. Periodic morphologic, cytogenetic and clonality evaluation after autologous peripheral blood progenitor cell transplantation in patients with lymphoproliferative malignancies. *Haematologica* 2002; **87**: 59–66.
18 Amigo ML, Del Canizo MC, Hernandez JM, Gonzalez MB, Gutiérrez N, Mateos MV *et al*. Clonal myelodysplastic cells present in apheresis product before transplantation. *Leukemia* 1998; **12**: 1497–1499.
19 Abruzzese E, Radford JE, Miller JS, Vredenburgh JJ, Rao PN, Pettenati MJ *et al*. Detection of abnormal clones in progenitor cells of patients who developed myelodysplasia after autologous transplantation. *Blood* 1999; **94**: 1814–1819.
20 Kroger N, Brand R, van Biezen A, Cahn JY, Slavin S, Blaise D *et al*. Autologous stem cell transplantation for therapy-related acute myeloid leukemia and myelodysplastic syndrome. *Bone Marrow Transplant* 2006; **37**: 183–189.
21 Anderson JE, Gooley TA, Schoch G, Anasetti C, Bensinger WI, Clift RA *et al*. Stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy. *Blood* 1997; **89**: 2578–2585.
22 Ballen KK, Gilliland DG, Guinan EC, Hsieh CC, Parsons SK, Rimm IJ *et al*. Bone marrow transplantation for therapy-related myelodysplasia: comparison with primary myelodysplasia. *Bone Marrow Transplant* 1997; **20**: 737–743.
23 Friedberg JW, Neuberg D, Stone RM, Alyea E, Jallow H, LaCasce A *et al*. Outcome in patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 1999; **17**: 3128–3135.
24 Yakoub-Agha I, De La Salmoniere P, Ribaud P, Sutton L, Wattel E, Kuentz M *et al*. Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: a long-term study of 70 patients—report of the French Society of Bone Marrow Transplantation. *J Clin Oncol* 2000; **18**: 963–971.