Haematologica 2000; 85:403-409
original paper

Transplantation & Cell Therapy

Incidence and characterization of secondary myelodysplastic syndromes following autologous transplantation

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Abstract

Background and Objectives. **Secondary myelodysplastic syndromes (sMDS) and secondary acute myeloid leukemias (sAML) have been observed after conventional chemo / radiotherapy and autologous hematopoietic stem cell transplantation. The aim of the present study was to analyze Spanish experience regarding the incidence and characteristics of sMDS and sAML following autologous transplantation.**

Design and Methods**. We obtained information from 7 institutions which perform autologous transplantation in Spain. Data from 1,081 and 1,411 patients who had received allogeneic and autologous transplantation, respectively, were available.**

Results**. None of the allografted patients had developed a sMDS / sAML so far. Thirteen cases of sMDS / sAML following autologous transplantation were reported. The mean age of these 13 patients at the time of transplantation was 40 years (range 16-58). Five had non-Hodgkin's lymphoma, 6 had Hodgkin's disease, 1 had acute myeloblastic leukemia and 1 had multiple myeloma. The crude overall incidence of sMDS / sAML was 0.9%. The incidence did not differ according to the source of progenitor cells (1% and 0.8% for bone marrow and peripheral blood, respectively). Cytogenetic analysis showed clonal abnormalities in 11 of the 13 cases. Patients with sMDS / sAML had received more doses of alkylating agents than non-sMDS patients (*p* = 0.0015). The median time between transplantation and diagnosis of sMDS / sAML was 28 months (range 1.5-63). This time was significantly longer for patients who received bone marrow than for those who received peripheral blood (45 versus 18 months, *p* = 0.01). Median overall survival after diagnosis of sMDS / sAML was 13 months.**

Interpretation and Conclusions. **The crude incidence of sMDS / sAML in our series was similar to other published incidences. We did not find any difference in incidence between patients who had received bone marrow or peripheral blood; however, the median time elapsed between transplantation and sMDS diagnosis was shorter when peripheral blood was infused. Higher doses of alkylating agents were associated with the appearance of sMDS / AML.**

Key words: secondary myelodysplastic syndromes, autologous transplantation, incidence, alkylating agents

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High-dose chemotherapy and autologous stem cell transplantation are being used with increasing frequency in the treatment of patients with lymphoma, myeloma, breast cancer and other diseases.[1-3] Secondary myelodysplastic syndromes (sMDS) and secondary acute myeloid leukemia (sAML) have been observed after conventional chemotherapy and radiotherapy for these disorders.[4,5] Since 1993, several studies have reported the development of sMDS and sAML in patients who undergo autologous transplantation.[5-14] This is an important late complication in patients receiving high-dose treatment that significantly compromises survival. There has been a great variability regarding the incidence of this complication in the literature.[7-15] The causes of sMDS and the factors which condition their development after transplantation are not well established. Strong evidence suggests that the therapy used in the treatment of the underlying disease is an important factor,[9,11,13] but the transplant procedure itself could play a role.[7,10] The aim of the present work was to ascertain the incidence of sMDS in Spain and to investigate which factors could contribute to their development.

Design and Methods

Data from seven Spanish institutions concerning 1,081 and 1,411 patients who had received allogeneic and autologous hematopoietic stem cells transplantation, respectively, were analyzed. The diagnosis of patients who underwent autologous transplanation was acute leukemia in 557 cases, non-Hodgkin's lymphoma in 308, Hodgkin's disease in 225, multiple myeloma in 189, chronic myeloid leukemia in 37 and solid tumors in 95 cases. Stem cells from peripheral blood were used in 852 patients and from bone marrow in the other 559 patients.

The following data were required for patients who developed a secondary MDS or AML: date of prima-

ry diagnosis, treatment received prior to transplantation, date of transplantation, conditioning regimen, source and dose of hematopoietic progenitor cells, outcome after transplantation, date of MDS/AML diagnosis, FAB subtype, presence of myelodysplastic features in bone marrow, cytogenetic results and, if the patient died, date and cause of death. Those cases in which sMDS or sAML could have been a relapse of the primary disorder were excluded from the study.

Because of the variability of chemotherapy regimens administered in order to evaluate the influence of alkylating agents received, a series of dose modules was considered: 600 mg/m^2 of cyclophosphamide, 36 mg/m^2 of melphalan, 12 mg/m^2 of mechlorethamine and 1,400 mg/m^2 of procarbazine. These doses are equivalent to one cycle of standard chemotherapy. The total dose of the alkylating agents was estimated as the sum of these modules. In order to compare the total dose of alkylating agents received by patients who developed MDS or AML with the dose received by patients who did not develop these complications, we selected a cohort of 214 patients from the total 1,411 who underwent autologous transplantation. They underwent autologous transplantation in a single institution. Diagnosis was acute leukemia in 17 cases, non-Hodgkin's lymphoma in 80, Hodgkin's lymphoma in 35, multiple myeloma in 25, chronic myeloid leukemia in 7 and solid tumors in 46 cases.

Cytogenetic analysis

Bone marrow cells were cultured for 24 hours according to standard procedures.[16] Chromosomes were G-banded with Wright's stain. Karyotypes are presented according to ISCN nomenclature.[17]

Table 1. Characteristics of 13 patients with MDS or AML following autologous transplantation.

Pt.	*Age/Sex*	*Diagnosis*	*Pre-transplant chemotherapy*	*Alkylating modules*	*Source of stem cells*	*Conditioning regimen*	*FAB subtype*	*Months since diagnosis*	*Months since transplant*	*Post-transplant treatment*
1	21/M	AML	DATO +Adr, ARA-C+ TG, COAP	2	BM	CTX + TBI	RAEB	73	62	NO
2	39/M	NHL	CHOP, VIA	8	BM	BEAM	RAEB	51	36	NO
3	43/*	HD	CMOPP, TNI, ABVD, MOPP-ABVD, CEP	36	PB	CBV	RA	155	18	NO
4	52/*	NHL	CHOP, CTX + Pred	39	PB	CTX + TBI	AML	83	24	NO
5	16/M	HD	MOPP, ABVD	24	BM	BEAM	AML	69	35	NO
6	43/M	HD	MOPP/ABVD, RT m MOP/ABV	16	BM	CBV	RA	97	63	NO
7	31/M	HD	RT mantle, CHOP + RT ABVD, Pm + VP-16 ESHAP	20	PB	CBV	AML	154	1.5	NO
8	34/F	NHL	CNOP, COP COPADM, CYM	8.5	PB	BEAM	RA	30	13	NO
9	56/M	NHL	CHOP, Mega-CHOP CTX	16	PB	BEAM	RA	29	10	NO
10	58/M	MM	VCMP, VBAP, IFN, VBAD	7	BM	BEM	RAEB-t	55	28	TG
11	23/M	HD	Rt mantle, ABVD, COPP ABVD, ESHAP	16	BM	CBV	RAEB	170	55	Ifos + MTZ Pelvic RT VCR + Epiru + Ifos
12	57/F	NHL	PROMACE/MOPP CTX	14.83	PB	BEAM	RAEB	39	27	NO
13	47/F	HD	MOPP/ABV mini-BEAM	8.5	PB	BEAM	RA	65	44	RT

*M: males; F: females; *unknown. AML: acute myeloblastic leukemia; NHL: non-Hodgkin's lymphoma. HD: Hodgkin's disease. MM: multiple myeloma. RA: refractory anemia. RAEB: refractory anemia with excess of blasts. RAEB-t: Refractory anemia with excess of blasts in transformation; BM: bone marrow; PB: peripheral blood. DATO: adriamycin, ara-C, thioguanine, Vincristine; COAP: Cyclophosphamide, vincristine, ara-C, prednisone; adr.: adriamycin; TG: thioguanine; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone; VIA: VP-16: ifosfamide, adriamycin; C-MOPP: cyclophosphamide, vincristine, procarbazine, prednisone; TNI: total nodal irradiation; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; MOPP: nitrogen mustard, vincristine, procarbazine, prednisone; CEP: CCNU, VP-16, prednimustine; Pred: prednisone; RT: radiotherapy; m: mediastinal; Pm: prednimustine; ESHAP: VP-16, ara-C, cisplatin, solumedrol; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; CNOP: cyclophosphamide, mitoxantrone, vincristine, prednisone; IFN: interferon; VCMP: vincristine, cyclophosphamide, melphalan, prednisone; VBAP: vincristine, BCNU, adriamycin, prednisone; VBAD: vincristine, BCNU, adriamycin, dexamethasone; PROMACE: cyclophosphamide, adriamycin, VP-16, methotrexate, prednisone; COP: cyclophosphamide, vincristine, prednisone; COPADM: cyclophosphamide, vincristine, methotrexate, adriamycin, prednisone; CYM: methotrexate, ara-C, CTX: cyclophosphamide; TBI: total body irradiation BEAM: BCNU, VP-16, ARA-C, melphalan; CBV: cyclophosphamide, BCNU, VP-16; Ifos: ifosfamide; VCR: vincristine; Epiru: epirubicin; MTZ: mitoxantrone; BEM: BCNU, VP-16, melphalan.*

Fluorescence in situ hybridization (FISH) studies

In order to explore whether or not clonal cells were already present in the infused product, when material was available, we used FISH to study the cryopreserved cells from patients who developed sMDS/AML. Cell pellets were resuspended in fresh fixative. After spreading, the slides were treated with RNAse and pepsin. The chromosomes were denaturated in 2xSSC and 70% formamide at 70ºC for 2 minutes followed by dehydration. The denaturation of the probes, the hybridization and the detection were performed according to manufacturer's instructions. Double color FISH was performed with pericentromeric probes for chromosome 7 (FITC) and 15 (TRITC) (Vysis, Stuttgart, Germany). The hybridization signals were analyzed on a Olympus BX60 fluorescence microscope equipped with a CCD camera and Cytovision software (Applied Imaging, Sunderland, UK).

Statistical analysis

Data were analyzed with the program SPSS for Windows. Student's t-test was used to compare the variables. Two sided *p* values of 0.05 were taken as statistically significant. Cumulative probability was estimated using the Kaplan-Meier method.

Results

No cases of sMDS or sAML were reported among the 1,081 patients who underwent allogeneic transplantation. By contrast, during the same time-period sMDS/sAML developed in 13 patients (10 sMDS and 3 sAML) following autologous transplantation with a crude overall incidence of 0.9%. None of these patients showed myelodysplastic features before transplantation. In 10 out of the 13 cases no chemotherapy or radiotherapy had been administered following autografting. Incidence according to diagnosis was as follows: 2.7% for Hodgkin's disease, 1.6% for non-Hodgkin's lymphoma, 0.5% for multiple myeloma and 0.2% for acute leukemia. The incidence was similar in patients reveiving bone marrow cells (1%) or peripheral blood cells (0.8%). Patients' characteristics are summarized in Table 1. The mean age at the time of transplantation for patients who developed sMDS or sAML was 40 years (range 16-58). Nine patients at the moment of sMDS/AML diagnosis presented with pancytopenia, two with cytopenia in two cell lines and two with abnormalities of only one cell line. Nine out of the 13 cases had reached normal peripheral blood values after transplantation, but the values had then become abnormal; the other 4 had persisting cytopenias from the time of transplantation. Bone marrow examination showed dyshemopoietic features affecting three lineages in 7 patients, two lineages in 2 patients and only the erythroid lineage was dysplastic in 1 patient. In the other three cases no dysplastic changes were found on bone marrow examination and the diagnosis of MDS was based on the presence of pancytopenia and cytogenetic abnormalities.

Cytogenetic analysis data were available for 12 cases and karyotypic aberrations were detected in 11 patients (Table 2). Abnormalities of chromosome 7 were present in 6 patients with monosomy 7 occurring in 3 of them. Alterations in chromosome 5 were found in 5 patients while chromosomes 6, 12 and 17 were abnormal in three patients each. No patient had rearrangement of chromosome band 11q23.

Table 2. Cytogenetic abnormalities.

Pts.	Cytogenetics
1	46,XY,-7,+mar 45,XY,-7,-12,+mar
2	45,XY,-4,del(5)(q?),-7, del(13)(q?),del(15)(q?),-17,+mar1,+mar2 45,XY,del(5)(q?),-7,-17,+mar2
3	Not done
4	46,XX,t(6;11)(q26;p15)
5	44,XY,del(5)(q14q34),-7,-12,-17,+der(12)t(12;17) (p13;q11.2)
6	46,XY,der(5)t(5;?)(q;?),-6,der(12)t(6;12)(q13;p13)+r
7	46,XY
8	46,XX,add(17)(p13)
9	46,XY 47,XY,+mar(D)
10	46,XY 45,XY,del(5)(q13;q31)der(7)(p),-9
11	46,XY 46,XY,del(6)(q16q24)
12	46,XX 44,XX,-5,dic(7;15)(p11;q11) 45,XX,-15,add(16)(p13)
13	46,XX 47,XX,+1,dic(1;7)(p11;q11),+8

Table 3. Interval from diagnosis and transplantation to the development of sMDS/sAML depending on the type of hematopoietic stem cells used.

	MDS/AML patients n = 13	*Bone marrow n = 6*	*Peripheral blood n = 7*	*p BM vs PB*
Months from transplantation	28 (1.5-63)	45 (28-63)	18 (1.5-44)	0.01
Months from diagnosis	69 (29-170)	71 (51-170)	65 (29-155)	0.47

Results are given as median (range). BM: bone marrow. PB: peripheral blood.

The total doses of alkylating agents were calculated as described in the *Design and Methods* section. Patients with sMDS/sAML received a median of 16 modules, a figure that is significantly higher than the dose received by the control group which did not develop myelodysplasia (7.5 modules; $p = 0.0015$). The median number of mononuclear cells infused in the 13 patients with secondary disease was similar to the number received by the control group (6.58 versus 5.59×10^8/kg; $p = 0.8$).

The median interval from the time of transplantation to the development of sMDS/sAML was 28 months, and interestingly this time was shorter (18

months) in patients who had received peripheral blood, than in patients who had received bone marrow (45 months) ($p = 0.01$). However, there were no differences between these two groups when we analyzed the time elapsed from the beginning of the treatment for the underlying disease (Table 3). It should be noted that the amount of modules of alkylating agents was similar in patients who received peripheral blood or bone marrow ($p = 0.19$).

The overall median survival from the time of sMDS/sAML diagnosis was 13 months. Four patients received treatment for sMDS/sAML: two received conventional induction chemotherapy with cytarabine and daunorubicin (3+7), and the other two underwent allogeneic bone marrow transplantation (one related and the other unrelated). The remainnig nine patients received only supportive care.

Follow-up data regarding 560 patients who underwent autologous transplantation in three of the seven institutions which participated in the study were reported. The median follow-up of this cohort was 30 months. Eight cases of sMDS/sAML were diagnosed in this group. The cumulative incidence of developing a sMDS/sAML was 3.1% at 5 years (Figure 1). Six out of the eight cases were diagnosed in a single institution (the center that designed the study). In this center a total of 214 transplant procedures were performed with a median follow up of 31.7 months. Cumulative incidence for this center was 6.12% at 5 years (Figure 2).

In order to explore whether or not the clonal alteration was already present in the progenitor cells used for transplant, we retrospectively analyzed cryopreserved cells from two patients by FISH. The first patient (previously reported[18]) had a clonal cytogenetic abnormality when she was diagnosed as having sMDS: 44,XX,-5,dic(7;15)(p11;p11). This karyotype was shown by FISH in the cryopreserved product used for the transplantation. By contrast, in the other patient (#13 in Table 1), although cytogentetics showed aberrations at the time of the sMDS diagnosis, when we analyzed the cryopreserved cells by FISH, only normal metaphases could be observed.

Discussion

Over the last few years several reports have appeared of sAML/sMDS under the heading of secondary MDS following hematopoietic stem cell transplantation.[6-15] However, it is open to question whether this complication is due to the transplantation procedure or to the previous chemotherapy used for the treatment of the underlying disease. The aim of this study was to explore the incidence of this complication in Spain and to investigate which factors contribute to its development.

Interestingly, none of the patients who underwent allogeneic transplantation developed sMDS/AML. This is consistent with other reports that show a lower incidence of this complicaction in allografts compared to autografts.[19] A possible explanation for this difference is that the cells used for transplantation were from a normal donor and they had not been previously exposed to any chemo/radiotherapy treatment.

sMDS/AML developed in 13 out of 1,411 patients following autologous transplantation. The crude incidence of sMDS/sAML in our series is similar to that reported by Taylor *et al.* and Laughlin *et al.*[20] but lower than that in other reports[7-11,13] (Table 4). However, when only patients with Hodgkin's disease or non-Hodgkin's lymphoma were analyzed, our incidence was even higher than that in other series (2.7% and 1.6% respectively). Our cumulative incidence results are similar to those in other reported series[10,14] and to the recently published data from the EBMT.[21] Interestingly, the cumulative incidence was higher in the institution which designed the study. This fact suggests that awareness about the problem facilitates the diagnosis of these malignancies. It is possible that sMDS after transplantation are occasionally interpreted as poor engraftment. Cytogenetic analysis can be useful in early detection of these disorders in patients with persistent or developing cytopenias following autologous transplantation.

A higher incidence of sMDS/sAML has been reported when peripheral blood cells are used as the source of progenitor cells.[7,8] In the present study incidence of secondary disease was similar in bone marrow or peripheral blood transplanted patients (1 and 0.8%, respectively). In our series, the median time from transplantation to sMDS/sAML diagnosis was similar to the time reported by other authors (Table 4) and similar

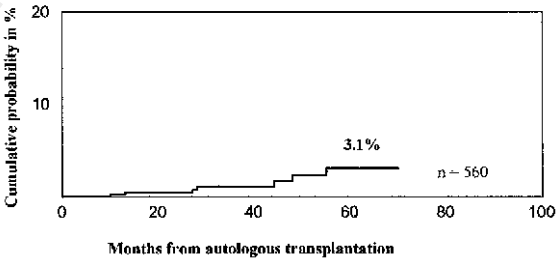

Figure 1. Cumulative probability of developing a sMDS / AML following autologous transplantation.

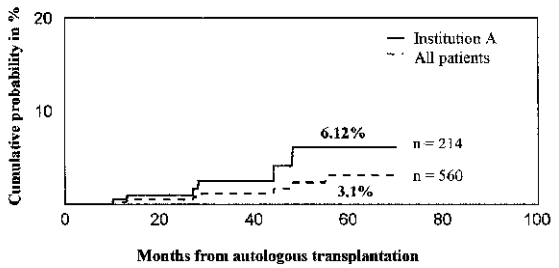

Figure 2. Cumulative probability of developing a sMDS / AML following autologous transplantation for the institution that designed the study (institution A) and for all the patients.

Table 4. Myelodysplasia after autologous transplantation.

Series	*No. transplanted*	*Cases of MDS + AML*	*Crude incidence*	*Time to MDS since transplantation* (range)*
Darrington *et al.*, 1994	249 (HD) 262 (NHL)	6 6	2.4 2.3	44 (13-74)
Miller *et al.*, 1994	206 (NHL and HD)	9	4.4	34 (5-60)
Stone *et al.*, 1994	262 (NHL)	20	7.6	31 (10-101)
Traweek *et al.*, 1994	275 (NHL and HD)	5	1.8	11 (8-37)
Govindarajan *et al.*, 1996	275 (MM)	7	2.5	24 (9-39)
Taylor *et al.*, 1997	114 (NHL and HD)	1	0.9	124
Pedersen-Bjergaard *et al.*, 1997	76 (NHL and HD)	6	7.9	13 (4-43)
André *et al.*, 1998	467 (HD)	8	1.7	21 (3-43)
Miligan *et al.*, 1999	4,998 (NHL and HD)	66	1.3	
Present series	308 (NHL)	5	1.6	25.5 (1.5-63)
	225 (HD)	6	2.7	

*MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma. MM: multiple myeloma. *Median in months.*

to the incubation period of the alkylating agents related to MDS. Interestingly, however, the median time elapsed between transplantation and MDS diagnosis was shorter when peripheral blood was infused rather than bone marrow. This is in accordance with the periods reported by other authors[7-11] (Table 5) and suggests that the source of progenitor cells can condition the evolution of these disorders. More cells are infused in peripheral blood stem cell transplantation and perhaps more clonal cells are also present in the infusion product, leading to a shorter incubation period.

In most cases of therapy-related MDS, outside the context of transplantation, a high degree of trilineage dysplasia is observed. In our cases of sMDS following transplantation, the diagnosis was suspected because of the presence of cytopenias. Some cases showed peripheral blood cytopenias and cytogenetic abnormalities but without marked myelodysplastic changes. This is in concordance with the data reported by Wilson *et al.*[22] who described two types of MDS following transplantation: indolent (few dysplastic changes) and aggressive MDS (more prominent dysplastic features). Another difference between sMDS following high dose chemotherapy and sMDS following conventional chemotherapy is the longer survival observed in the former group. In our series of transplanted patients the median overall survival from diagnosis of sMDS was 13 months, a figure similar to that reported by Miller *et al.* (10 months) and Stone *et al.* (9.2 months). In the published series of sMDS attributed to chemotherapy, survival was shorter, being approximately 6 months.[4,5]

Table 5. Months since transplantation to sMDS / sAML reported in the literature depending on the type of hematopoietic stem cells used.

Series	*Bone marrow*	*Peripheral blood*
All patients[7-11]	35 (8-104)	24 (5-46)
Miller *et al.*[7]	39.5 (11-60)	9 (5-35)
Traweek *et al.*[8]	18.5 (8-29)	21 (6-37)
Darrington[10]	43 (13-75)	41 (27-46)

Results are given as median (range).

In our patients, chromosomes 7 and 5 were most frequently affected. The changes detected were similar to those previously described for therapy-induced or post-transplantation hematopoietic disease.[5,7-11,23–25] These alterations have been strongly associated with the use of alkylating agents. All patients had received alkylating agents before transplantation or during their conditioning regimen. Abnormalities in chromosomes 12 have also been observed MDS after autologous transplantation.[7,8,10] In our series two of the three cases (#5 and 6) had a breakpoint on 12p13. This is the region in which ETV-6 gene is located. This gene has been related to several hematologic malignancies such as MDS, acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL).[26,27] However, the relationship between the 12p13 region and therapy-related MDS has not been previously described. Three patients (#4, 6 and 11) had structural abnormalities of chromosome 6q. Interstitial deletions of 6q have been reported on B-cell malignancies such as non-Hodgkin's lymphomas and ALL.[28,29] However, these abnormalities are less common in MDS.[28,30] Two cases (#12 and 13) had dicentric chromosomes, both involving chromosome 7. The presence of dicentric chromosomes has been related to previous therapy with alkylating agents.[31] However, we did not find abnormalities in 11q23, involving the MLL gene, that have been related to the use of topoisomerase II inhibitors.[4,5]

Discordant data have been reported regarding whether the therapy received prior to a transplant or the transplant procedure itself – conditioning regimen – are responsible for secondary disease. Darrington *et al.* suggested that patients receiving a preparative regimen including total body irradiation were at higher risk of MDS while Govindarajan *et al.*[11] pointed out that prolonged therapy with alkylating agents is the most important risk factor for the development of these complications although other authors have not confirmed these data.[7,10,15] In our study, patients who developed a sMDS/sAML had received a significantly higher dose of alkylating agents. This fact suggests that previous therapy (including drugs and growth factors used to mobilize

progenitor cells) is important in the development of the secondary disease. Accordingly, prolonged exposure to alkylating agents should be avoided in patients who are candidates for autologous transplantation.

One of our aims was to explore whether the abnormal clone was present prior to transplant or appeared after the procedure. Using FISH we demonstrated that the clonal alteration was already present in the stored cells used for transplantation in one of the two studied patients. The same observation was recently reported by Abruzzese *et al.*[32] This indicates that, at least in some cases, the malignant clone is present in the infusion product although it cannot always be observed. We consider that karyotyping should be carried out before hematopoietic transplantation in heavily pretreated patients.

Contributions and Acknowledgments

MCC and MLA were responsible for the conception of the study and wrote the paper. JMH performed most of the cytogenetic analysis. GS, RN, EC, AA, BC and RM cared for patients. We acknowledge the help of Prof. J.F. San Miguel in reviewing the manuscript.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Received on May 18, 1999; accepted January 4, 2000.

Potential implications for clinical practice

- Prolonged exposure to alkylating agents should be avoided in patients who are candidates for autologous transplantation.
- A cytogenetic analysis must be performed to diagnose secondary MDS following autologous transplantation.

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