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Secondary myelodysplastic syndrome/acute myeloid leukemia after autologous transplantation

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High-dose chemotherapy followed by autologous bone marrow (BM) or peripheral blood (PB) stem cell transplantation (SCT) are being used with increasing frequency in the treatment of hematopoietic malignancies and solid neoplasms. The improvement in survival after hematopoietic stem cell transplantation has drawn increased attention to late complications in long-term survivors. The increased risk of developing second malignancies is essentially multi-factorial, related to carcinogenic effects of chemotherapy and radiotherapy as well as possible enhanced susceptibility to cancer development related to underlying immunologic deficiencies impairing cancer surveillance.[1] The clinical course of secondary myelodysplastic syndrome/acute myeloid leukemia (sMDS/AML) is typically progressive and generally resistant to conventional therapies used for leukaemia arising *de novo*.[2,3] Several studies suggest that chemo-radiotherapy administered before transplant contributes to the subsequent development of sMDS/AML after APBSCT, in fact sMDS/AML has occurred infrequently after allogeneic transplantation.[4,5] These data were confirmed by Abruzzese et al. who observed that cytogenetic abnormalities detected by FISH analysis at the time of MDS diagnosis after autologous transplant were often present in the pre-high dose chemotherapy specimens.[6] The latency period between primary diagnosis and therapy-related disease may vary from months to several years, and it may be dependent on the cumulative dose or dose intensity of the previous chemo-radiotherapy and the exposure to specific agents.

The estimated cumulative probability of sMDS/AML after autologous transplantation for lymphoproliferative disease ranges from 3,8% to 18% at 5 years,[7,8] and sMDS/AML is increasingly recognised as a major cause of non relapse-related mortality in this population.[9-11]

Classically alkylating agents, radiation or both caused losses or deletion of chromosomes 5 and 7, while topoisomerase II inhibitors led to abnormalities of chromosome 11 after transplant.[12] The latency period is shorter after topoisomerase II inhibitors (2-3 years) and longer after alkylating agents (3-8 years). Alkylating agents related leukemia is characterised by pre-leukemic phase and trilinear dysplasia, while secondary leukemia related to topoisomerase II inhibitors are not preceded by a preleukemic phase.[5]

Metayer *et al.* identified type and intensity of pre-transplant chemotherapy including meclorethamine and chlorambucil as an important risk factor of sMDS/AML in patients affected by lymphoproliferative disorders. They also reported an apparent association between sMDS/AML and high dose TBI (>13.2Gy) as conditioning regimen.[13]

On the contrary in different retrospective studies of lymphoma patients receiving ASCT, multivariate analysis suggested TBI to be associated with an increased risk of sMDS/AML even at lower doses of 13.2 Gy.[4,14,15]

Several authors reported that fludarabine exposure was a significant risk factor for the development of sMDS/AML after APBSC.

Recently in patients affected by CLL, Milligan et al. report a high incidence (12.4%) of sAML/MDS after ASCT hypothesising as potential causative factors fludarabine, low cell dose and transplant conditioning regimen.[16]

In patients with indolent lymphoma a moderate increase of secondary haematological malignancies after myeloablative radio-chemotherapy and

Table 1. Characteristics of patients.

	Values
No. of patients	142
Median age (range)	44.5 (17-63)
Gender (M/F)	82/60
Diagnosis	
NHL	81
MM	30
HD	26
CLL	5
Type of treatment	
Standard chemotherapy	142
Second line chemotherapy	53
Second line & radiotherapy	7
Second line & Rituximab	26
Second line & PBSCT	18
Third line chemotherapy or more	26
Status at transplant	
CR	67
PR	63
PD	12
Conditioning regimen	
BuMel	77
BuCy2	21
BEAM	23
HDMel	15
MitMel	6
Type of harvest	
Unselected	103
$CD34^+$ selected	39

M: male, F: female, NHL: Non Hodgkin's Lymphoma, MM: Multiple Myeloma, HD: Hodgkin's disease, CLL: Chronic Lymphocitic Leukemia, PBSCT: Peripheral Blood Stem Cell Transplantation, CR: Complete Remission, PR: Partial Remission, PD: Progression Disease, BuMel: Busulphan and Melphalan, BuCy2: Busulphan and Cyclophosphamide; BEAM: BCNU, Etoposide, Aracytin and Melphalan, HDMel: High Dose Melphalan, MitMel: Mitoxantrone and Melphalan.

autologous stem cell transplantation was observed when compared to conventional chemotherapy alone.[17] In patients affected by Hodgkin's Lymphoma Forrest et al. reported an increased risk of developing second neoplasm, although no difference in the incidence was found between patients undergoing conventional chemotherapy alone or followed by ASCT, at least during the first decade after therapy.[18]

The exact frequency of sMDS/AML and secondary solid neoplasm after ASCT remains therefore uncertain and needs to be determined more precisely on the basis of a prospective evaluation of ASCT versus conventional chemotherapy.

Experience of UCSC-Roma

The aim of this study is to report the real incidence of sMDS/AML due to conventional therapy followed by APBSCT in a group of selected patients according to stringent inclusion/exclusion criteria and to investigate which factors could contribute to their development.

Between January 1988 and December 2004, 323 patients were submitted to autologous SCT for haematological malignancies in our Division of Haematology. Patients developing secondary MDS/AML were identified from a cohort of 142 patients receiving autologous transplant for lymphoproliferative disorders at our transplant centre. Absence of cytogenetic abnormalities before transplantation was mandatory. Patients affected

Table 2. Characteristics of patients affected by sAML/MDS.

UPN	*78*	*103*	*104*
Primary hematologic disease	NHL	CLL	NHL
Age	45	60	26
Gender (M/F)	M	M	M
Prior chemotherapy	CHOP, FLU-ID, MiCMA, HD-VP-16, HD-CTX	FLU, HD-CTX	CODOX-M/IVAC, MiCMA, IEV
Prior radiotherapy	No	No	No
Prior monoclonal antibody	Rituximab	No	Rituximab
Disease status at transplant	PD	CR	PR
Conditioning regimen	BuMel	MitMel	BuMel
Type of harvest	uPBSCT	UPBSCT	uPBSCT
Secondary hematological disease	AML	MDS	MDS
Cytogenetic and/or FISH abnormalities	n.e./-7	46XY,del(20)(q11)/ n.d.	n.e./-7
Time from diagnosis to sAML/MDS (months)	56	24	61
Time from transplant to sAML/MDS (months)	6	15	41
Survival after sAML/MDS with or without chemoterapy	Dead 6 months after HD-cytarabine	Alive 35 months Allogeneic transplant are ongoing	alive 7 months In CR after Allogeneic transplant

NHL: Non Hodgkin's Lymphoma, CLL: Chronic Lymphocitic Leukemia, M: male, PD: Progression Disease, CR: Complete Remission, PR: Partial Remission, BuMel: Busulphan and Melphalan, MitMel: Mitoxantrone and Melphalan, uPBSCT: unselected Peripheral Blood Stem Cell Transplantation, AML: acute myeloid leukemia, SMD: myelodysplastic syndrome, n.e.: not evaluable.

Table 3. Resuts of univariate analysis (sAML/MDS).

Variable	*Patients with sAML/MDS: Number (%)*	*Patients without sAML/MDS: Number (%)*	*p**
Diagnosis			
HD	0 (0)	26 (100)	0.045
NHL	2 (2.5)	79 (97.5)	
CLL	1 (20)	4 (80)	
MM	0 (0)	30 (100)	
Age			
Mean (SD)	43.67 (17.04)	44.17 (12.33)	0.960
Gender			
Males	3 (3.7)	79 (96.3)	0.143
Females	0 (0)	60 (100)	
Disease status at PBSCT:			
PD	1 (8.3)	11 (91.7)	0.151
PR	1 (1.6)	62 (98.4)	
CR	1 (1.5)	66 (98.5)	
Type of harvest			
Unselected	3 (2.9)	100 (97.1)	0.269
$CD34^+$ selected	0 (0)	39 (100)	
Radiotherapy			
Yes	0 (0)	8 (100)	0.698
No	3 (2.2)	131 (97.8)	

NHL: Non Hodgkin's Lymphoma, MM: Multiple Myeloma, HD: Hodgkin's disease, CLL: Chronic Lymphocitic Leukemia, PBSCT: Peripheral Blood Stem Cell Transplantation, CR: Complete Remission, PR: Partial Remission, PD: Progression Disease.

by multiple myeloma (MM), Non Hodgkin's Lymphoma (NHL), Hodgkin's disease (HD) undergoing double transplant for whatever reason, entered the study after the second transplant. Follow-up was granted until progression disease requiring treatment, development of secondary MDS/AML or death. Characteristics of patients are shown in Table 1.

Periodical follow-up, including physical examinations, complete peripheral blood counts, morphological and cytogenetic analyses of bone marrow were routinely performed before and after transplant in all patients. FISH analysis was not performed routinely after transplant. Secondary AML and MDS were classified according to WHO classification. A univariate survival analysis was conducted using the Kaplan Meyer curves, to assess differences in time to the development of MDS for the covariates: gender, diagnosis, chemotherapy and radiotherapy before conditioning regimen, disease status at PBSCT, type of harvest (selected or unselected PBSC).

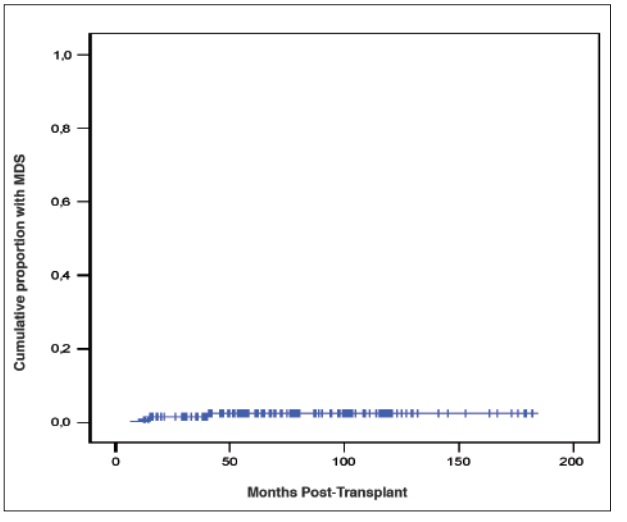

Figure 1. Cumulative proportion of disease free survivors with sMDS/AML in 142 patients transplanted for LH, LNH, LLC and MM.

Morphological evaluation of bone marrow was performed on samples obtained from 142 patients for a total of 376 controls. A total of 258 cytogenetic controls and 43 FISH analysis were analyzed. One-hundred-forty-two patients were followed for a median of 47 months (range 6-182); thirty patients showed progression disease requiring treatment, among them 2 patients treated with additional chemotherapy and/or radiotherapy developed sMDS/AML at 41 and 84 months after ASCT and were not included in the analysis.

Out of 142 patients included in the study, 3 (2.1%) developed sMDS/AML at 6, 15 and 41 months after PBSCT respectively for mantle cell lymphoma, Chronic Lymphocitic Leukemia (CLL) and diffuse large B cell lymphoma (Table 2). One patient died 6 months after diagnosis of sAML, two patients receiving allogeneic stem cell transplantation at 7 and 35 months respectively after diagnosis of sMDS, are alive at 7 and 3 months respectively after transplant.

The projected incidence of sMDS/AML at 5 years after transplantation was 2.48%±2.88% (95% CI) (Figure 1).

At univariate analysis, diagnosis was the only variable significantly associated with the development of sMDS/AML, with higher incidence rates in patients with CLL and NHL, while there were no differences by gender, type of harvest, disease status at PBSCT, type of drugs and radiotherapy before conditioning regimen (Table 3). At multivariate analysis, the variables associated to sAML/MDS were diagnosis and status disease at SCT.

Thus we report the lowest incidence of sMDS/AML after ASCT reported in literature for lymphoproliferative malignancies. Major reasons could be ascribed to the stringent inclusion/exclusion criteria leading to establish the real incidence of sMDS/AML due to chemo-radiotherapy used before transplant procedure excluding a number of confounding factors as :

- the use of chemo-radiotherapy or biological response modifiers after autologous transplant for progression disease requiring treatment;
- cytogenetic abnormalities before conditioning regimen;
- morphological cell atipia and dysplastic feature commonly observed during the first months after aPBSCT leading to misdiagnosis of low risk MDS (refractory anemia; refactory anemia with ringer sideroblast, refractory cytopenia with multilineage dysplasia, refractory cytopenia with multilineage dysplasia with riger sideroblasts).[19,20]

Although many risk factors have been identified for the development of secondary neoplasm after autologous transplant many of them are still controversial. As long-term survival and awareness increase all methods able to prevent or reduce these complications should be pursued.

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