

Long-term follow-up of autologous stem cell transplantation after intensive chemotherapy in patients with myelodysplastic syndrome or secondary acute myeloid leukemia.

Sophie Ducastelle, Lionel Adès, Claude Gardin, Hervé Dombret, Thomas Prébet, Eric Deconinck, Bernard Rio, Xavier Thomas, Stephan Debotton, Agnès Guerci, et al.

► **To cite this version:**

Sophie Ducastelle, Lionel Adès, Claude Gardin, Hervé Dombret, Thomas Prébet, et al.. Long-term follow-up of autologous stem cell transplantation after intensive chemotherapy in patients with myelodysplastic syndrome or secondary acute myeloid leukemia.. *Haematologica*, Ferrata Storti Foundation, 2006, 91 (3), pp.373-6. <inserm-00473474>

HAL Id: inserm-00473474

<http://www.hal.inserm.fr/inserm-00473474>

Submitted on 28 Dec 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Long-term follow-up of autologous stem cell transplantation after intensive chemotherapy in patients with myelodysplastic syndrome or secondary acute myeloid leukemia

Sophie Ducastelle
Lionel Adès
Claude Gardin
Hervé Dombret
Thomas Prêbet
Eric Deconinck
Bernard Rio
Xavier Thomas
Stephan Debotton
Agnès Guerci
Nicole Gratecos
Aspasia Stamatoullas
Nathalie Fegueux
François Dreyfus
Pierre Fenaux
Eric Wattel

We report on the outcomes of 53 patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia secondary to MDS, autografted in first complete remission. Five (9.4%) died from the procedure whereas hematological reconstitution occurred in all the remaining patients. Forty patients (75%) relapsed, with 87.5% of the relapses occurring within 2 years of the autologous transplant. With a median follow-up of 6.2 years, the median actuarial disease-free survival and overall survival were 8 and 17 months after autograft, respectively. Karyotype was the only prognostic factor for disease-free and overall survival. The eight survivors (15%), including two patients with unfavorable or intermediate karyotype, remained in first complete remission 50⁺ to 119⁺ months after transplantation and are probably cured.

Key words: myelodysplastic syndrome, intensive chemotherapy, autologous stem cell transplantation.

Haematologica 2006; 91:373-376

©2006 Ferrata Storti Foundation

From the Service d'Hématologie, Pavillon E, CHU, Hôpital Edouard Herriot, Lyon (SD, TP, XT, EW), Service d'Hématologie, CHU, Hôpital Saint-Louis, Paris (LA, HD), Service d'Hématologie, CHU, Hôpital Avicenne Bobigny (CG), Service d'Hématologie, CHU, Besançon (ED), Service d'Hématologie, CHU, Hôtel Dieu, Paris (BR), Service des Maladies du Sang, CHU, Lille (SD), Service d'Hématologie, CHU, Nancy (AG), Service d'Hématologie, CHU, Nice (NG), Service d'Hématologie, Centre Henri Baecquerel, Rouen (AS), Service d'Hématologie, CHU, Montpellier (NF), Service d'Hématologie, CHU, Hôpital Cochin, Paris (FD), Oncovirologie et Biothérapies, CNRS UMR 5537, Centre Léon Bérard, Lyon, France (EW).

Correspondence:
Eric Wattel, Service d'Hématologie, Pavillon E, hôpital Edouard Herriot, 5, place d'Arsonval, 69437 Lyon Cédex 03, France.
E-mail: wattel@lyon.fnclcc.fr

Autologous stem cell transplantation (ASCT) is becoming an accepted treatment for patients with high-risk myelodysplastic syndromes (MDS) in complete remission who lack an HLA-identical sibling. Although ASCT can be performed in about 60% of patients with MDS who obtain a complete remission after intensive chemotherapy,¹ their long-term outcome is still unclear because most previous reports on ASCT in MDS, especially in prospective studies, have had a relatively short follow-up.¹⁻¹⁰ Therefore, it remains unknown whether or not autografting can prolong complete remission duration in at least some MDS patients. Here we report the outcomes of 53 high-risk MDS patients autografted in first complete remission of whom 45 (85%) were autografted 4 years before the last analysis of outcome.

Design and Methods

Between March 1992 and March 2001, 53 MDS patients who lacked an HLA identical sibling and had achieved complete remission after intensive chemotherapy were autografted white in first complete remission. Induction chemotherapy consisted of intensive anthracycline-AraC chemotherapy, either alone (MA protocol, 14 patients) or combined with quinine (MAQ protocol, 11 patients)¹¹ or fludarabine (FAM protocol, 5 patients) or etoposide (9 patients)⁹ and/or granulocyte colony-stimulating factor (14 patients).⁷ Remission status was assessed

according to International Working Group (IWG) criteria.¹² Autografts were performed as already described.¹ Seventeen patients received autologous bone marrow and 36 autologous peripheral stem cells. The intervals for overall survival, disease-free survival, relapse rate and risk of transplant-related mortality were calculated from the time of the ASCT. Comparisons were made with the chi squared test. Survival curves were drawn by the Kaplan Meier method,¹³ and compared using the log rank test.¹⁴ Prognostic factors were assessed using the Cox model.¹⁵ The 53 autografted MDS patients were prospectively registered. For the present study, March 2001 was chosen as the accrual cut-off date in order to provide sufficient follow-up at the reference date of 1 June 2003. Toxic deaths were defined as all deaths occurring within the 3 months after ASCT. Long-term survivors were defined as patients having survived more than 4 years after transplantation. Relapses occurring within the 6 months after transplantation were defined as early relapses. To avoid time-associated biases in this series of patients included over a 9-year period, long-term survivors were compared with patients included at least 4 years before the reference date of 1 June 2003.

Results and Discussion

The median age of the 53 patients was 52 years (range: 18-65). Twenty-nine had acute myeloid leukemia (AML) secondary to MDS

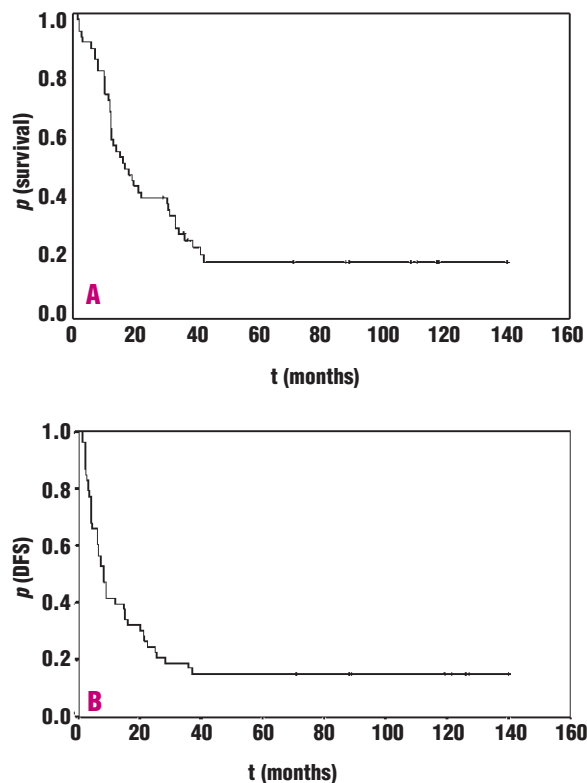


Figure 1. A Survival and B disease free survival of the 53 autografted MDS patients.

(55%), 15 had refractory anemia with excess blasts (RAEB) in transformation (RAEB-T) (28%) and 9 had RAEB (17%). Thirteen patients (24%) had therapy-related MDS. Overall, 45 patients were successfully karyotyped. In the 18 non-AML patients who were successfully karyotyped, 3 and 15, respectively belonged to the high-risk and intermediate-2 risk subgroups of the International Prognostic Scoring System.¹⁶ Bone marrow and peripheral blood stem cells were harvested 0.5 to 5 months (median 2.3 months) after achieving complete remission and the ASCT was performed 1 to 7 months (median 3.7 months) after achievement of complete remission. The conditioning regimens were a combination of cyclophosphamide and busulfan in 31 patients, cyclophosphamide, busulfan and etoposide in 14 patients, and cyclophosphamide plus total body irradiation in 8 patients. Five patients (9.4%) died from the procedure. These early deaths, occurring in two bone marrow recipients and three peripheral blood stem cell recipients, were characterized by a high proportion of unfavorable karyotypes: 3/5 versus 4/40 ($p=0.021$). Hematologic reconstitution occurred in all remaining 48 patients, without significant differences between the three conditioning regimens.

Forty patients (75%) relapsed 3.1 to 37 months (median 8 months) after transplantation and 8 (15%) were still in complete remission after 50 to 119 months (median 80 months). In three of the 40 patients in relapse, a second prolonged complete remission was

Table 1. Initial characteristics of autografted MDS patients surviving than or more than 48 months.

	Survival		p
	<48 months (37 patients)	≥ 48 months (8 patients)	
Mean age	48	47	ns
Sex (male/female)	11/26	6/2	0.024
FAB at diagnosis (%)			ns
Refractory anemia	7 (19)	0 (0)	
Refractory anemia with excess blasts	17 (46)	4 (50)	
Refractory anemia with excess blasts in transformation	13 (35)	3 (37)	
Chronic monomyelocytic leukemia	0 (0)	1 (13)	
FAB at the onset of treatment (%)			ns
Refractory anemia with excess blasts	6 (16)	1 (13)	
Refractory anemia with excess blasts in transformation	10 (27)	2 (24)	
Acute myeloma leukemia	21 (57)	5 (63)	
Abnormal karyotype (n=38) (%)			ns
Normal	13 (43)	5 (72)	
-7 (single)	2 (7)	0 (0)	
Other single abnormalities	10 (33)	1 (14)	
Complex	5 (17)	1 (14)	
Risk group, in non-AML cases according to the IPSS (at treatment onset) (n=15) (%)			ns
High	10 (83)	2 (67)	
Intermediate-2	2 (17)	1 (33)	
Hematologic findings			
White cell count (mean, $10^3/\text{mm}^3$)	4.1	6.2	ns
Bone marrow blasts (mean percentage)	36.1	40.13	ns
Mean interval from diagnosis to treatment (months)	7.3	4.7	ns
Mean interval from complete remission to ASCT (months)	3.7	4.2	ns
Yields of harvested cells			
CFU-GM ($10^4/\text{kg}$)	30	48	ns
CD34+ cells ($10^6/\text{kg}$)	5	4.1	ns

obtained by intensive chemotherapy followed by allogeneic stem cell transplantation from an unrelated donor. All remaining 37 relapsed cases died from progressive disease. The Kaplan-Meier estimate of overall survival was $68\pm 7\%$ at 12 months, $40\pm 7\%$ at 24 months, $26\pm 6\%$ at 36 months, and $19\pm 6\%$ at 48 months (Figure 1). The Kaplan-Meier estimate of disease-free survival was $38\pm 7\%$ at 12 months, $21\pm 6\%$ at 24 months, $15\pm 5\%$ at 36 and 48 months (Figure 1). The

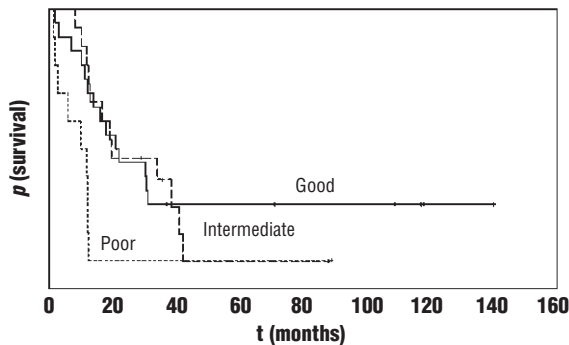


Figure 2. Survival as a function of cytogenetic abnormalities.

median disease-free and overall survivals were 8 and 17 months after autograft, respectively. In Cox analysis, karyotype was the only prognostic factor for outcome of the autograft (Figure 2), patients with favorable cytogenetic findings having a better overall survival than others (relative risk 0.33, 95% confidence interval 0.14-0.78, $p=0.011$). Only cytogenetic abnormalities significantly influenced disease-free survival (relative risk 0.36, 95% confidence interval 0.154-0.839; $p=0.018$).

Fifteen patients who achieved complete hematologic reconstitution after ASCT relapsed within 6 months of transplantation. These early relapses were characterized by a high proportion of unfavorable karyotypes, according to the IPSS classification (41.7 vs. 9.5%, $p=0.04$).¹⁶ All three patients with monosomy 7 relapsed at 2, 3, and 4 months after ASCT, while five of the seven patients with complex abnormalities relapsed at 2, 2.6, 4, 4, and 28.1 months.

ASCT was performed 25 to 127 months before the reference date of analysis (median 74 months), thus providing a sufficient follow-up to estimate the proportion of long-term survivors in this series of 53 autografted MDS patients. Among the 48 patients who achieved hematologic reconstitution after ASCT, 35/40 relapses (87.5%) occurred in the 2 years after ASCT, while the remaining five were diagnosed 25, 26, 28, 36, and 37 months after transplantation. The eight patients who remained alive in first complete remission 50+ to 119+ months (median 89 months) after ASCT were probably cured. The only difference between the long-term survivors and the other patients was the significantly higher proportion of females among long-term survivors (6/8 vs. 15/45, $p=0.047$). Time-dependent factors could have affected the outcome of MDS patients autografted at distinct occasions over the 9-year period of the study. We, therefore, next compared initial characteristics and outcomes of the eight long-term survivors with those of the 37 other cases autografted 4 years before the last outcome analysis (Table 1). Again, the only difference between long-term survivors and other patients was the higher proportion of females in the former group. All but two long-term survivors were females, whereas only 11 of the 37 patients who survived less than 4 years were females ($p=0.029$). Of interest, of the seven

successfully karyotyped long-term survivors with persistent complete remission after ASCT, one had a complex karyotype, one had trisomy 8 and five had a normal karyotype.

The main goal of our study was to assess the outcome of autografted MDS patients after a sufficient follow-up. We thus focused our analysis on 53 patients prospectively registered between March 1992 and March 2001 in 11 French centers; the median follow-up of the study group was 6.2 years. As our analysis focused on patients actually autografted, overall survival and disease-free survival were calculated from ASCT rather than from the time of achieving complete remission. Karyotype was the only prognostic factor influencing both overall survival and disease-free survival. In contrast, there was no significant difference in the distribution of cytogenetic abnormalities between long-term survivors and other patients. Interestingly, of the seven long-term survivors who were successfully karyotyped, one had a complex karyotype and one had trisomy 8. These two patients were, respectively, in first complete remission 50+ and 68+ months after ASCT, showing for the first time that intensive chemotherapy followed by ASCT can cure patients with high-risk MDS and an unfavorable karyotype.

Prolonged follow-up revealed that the majority of autografted MDS patients (75%) relapsed and, at 3 years, the Kaplan-Meier estimate of overall survival and disease-free survival was, respectively, $23\pm 6\%$ and $15\pm 5\%$. More than 85% of the relapses occurred in the 2 years following transplantation. Cytogenetic abnormalities were able to predict these early relapses which were three times more common in patients with unfavorable karyotypes. By contrast, relapses occurring after 6 months could not be correlated with FAB classification, age, sex or karyotype. As shown in Figure 1, the Kaplan-Meier overall survival curve reached a plateau at 40 months after ASCT. No relapse occurred after this period and the median duration of complete remission of the eight long-term survivors was 89+ months. The unique particular characteristic of these patients was that most were females (75%). In our previous experience of 71 MDS patients in complete remission after intensive chemotherapy without ASCT, who had over 4 years follow-up, less than 6% of the patients remained in first complete remission.¹⁷ Here, 8/45 (18%) of autografted MDS patients with over 4 years follow-up experienced prolonged survival in complete remission.

In conclusion, in this long-term study, 15% of high-risk MDS patients in first complete remission, including some with an unfavorable karyotype, experienced prolonged disease-free survival and were probably cured after ASCT. This proportion of long-term survivors appears to be higher than that obtained with consolidation chemotherapy in our historical series.¹⁷ Other treatment approaches might, however, provide better long-term results. Using intensive chemotherapy with granulocyte colony-stimulating factor priming followed by consolidation chemotherapy, Hofman *et al.* reported encouraging results with a 16% probability of patients in complete remission retaining this status after 60

months.¹⁸ Together, these results suggest that intensified consolidation in patients with MDS may increase the proportion of long-term, disease-free survivors, although therapeutic approaches still need to be optimized and/or supplemented in order to decrease the relapse rate.

PF and EW conceived the study. The study was performed in 12 groups under the direction of CG, HD, ED, BR, XT, SD, AG, NG, AS, NF, FD, and PF. SD, TB, and LA collected and analyzed the data with PF and EW. EW wrote the manuscript with contributions from other authors. The authors declare that they have no potential conflicts of interest.

This work was supported by a grant from the Association pour la Recherche sur le Cancer. We thank Céline Paul for technical assistance and Marie-Dominique Reynaud for assistance in preparing the manuscript.

Manuscript received September 19, 2005. Accepted December 27, 2005.

References

1. Wattel E, Solary E, Leleu X, Dreyfus F, Brion A, Jouet JP, et al. A prospective study of autologous bone marrow or peripheral blood stem cell transplantation after intensive chemotherapy in myelodysplastic syndromes. Groupe Français des Myelodysplasies. Group Ouest-Est d'Etude des Leucémies Aigues Myeloides. *Leukemia* 1999; 13: 524-9.
2. Laporte JP, Isnard F, Lesage S, Fenaux P, Douay L, Lopez M, et al. Autologous bone marrow transplantation with marrow purged by mafosfamide in seven patients with myelodysplastic syndromes in transformation (AML-MDS): a pilot study. *Leukemia* 1993; 7:2030-3.
3. Demuyneck H, Delforge M, Verhoef GE, Zachee P, Vandenberghe P, Van den Berghe H, et al. Feasibility of peripheral blood progenitor cell harvest and transplantation in patients with poor-risk myelodysplastic syndromes. *Br J Haematol* 1996;92:351-9.
4. Carella AM, Dejana A, Lerma E, Podestà M, Benvenuto F, Chimirri F, et al. In vivo mobilization of karyotypically normal peripheral blood progenitor cells in high-risk MDS, secondary or therapy-related acute myelogenous leukaemia. *Br J Haematol* 1996;95:127-30.
5. Oosterveld M, Muus P, Suci S, Koller C, Verhoef G, Labar B, et al. Chemotherapy only compared to chemotherapy followed by transplantation in high risk myelodysplastic syndrome and secondary acute myeloid leukemia; two parallel studies adjusted for various prognostic factors. *Leukemia* 2002;16:1615-21.
6. Oosterveld M, Suci S, Verhoef G, Labar B, Belhabri A, Aul C, et al. The presence of an HLA-identical sibling donor has no impact on outcome of patients with high-risk MDS or secondary AML (sAML) treated with intensive chemotherapy followed by transplantation: results of a prospective study of the EORTC, EBMT, SAKK and GIMEMA Leukemia Groups (EORTC study 06921). *Leukemia* 2003;17:859-68.
7. Gardin C, Chaibi P, de Revel T, Rousselot P, Turlure P, Miclea JM, et al. Intensive chemotherapy with idarubicin, cytosine arabinoside, and granulocyte colony-stimulating factor (G-CSF) in patients with secondary and therapy-related acute myelogenous leukemia. *Club de Reflexion en Hématologie. Leukemia* 1997;11:16-21.
8. de Witte T, Hermans J, Vossen J, Bacigalupo A, Meloni G, Jacobsen N, et al. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol* 2000;110:620-30.
9. de Witte T, Suci S, Verhoef G, Labar B, Archimbaud E, Aul C, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. *Blood* 2001;98:2326-31.
10. De Witte T, Van Biezen A, Hermans J, Labopin M, Runde V, Or R, et al. Autologous bone marrow transplantation for patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia following MDS. Chronic and Acute Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. *Blood* 1997; 90:3853-7.
11. Wattel E, Solary E, Hecquet B, Caillot D, Ifrah N, Brion A, et al. Quinine improves the results of intensive chemotherapy in myelodysplastic syndromes expressing P glycoprotein: results of a randomized study. *Br J Haematol* 1998;102:1015-24.
12. Cheson BD, Bennett JM, Kantarjian H, Pinto A, Schiffer CA, Nimer SD, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood* 2000;96:3671-4.
13. Kaplan E, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
14. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc* 1972;135:185-206.
15. Cox DR. Regression models and life-tables (with discussions), Series B. *J R Stat Soc* 1972;34:187-220.
16. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079-88.
17. Wattel E, De Botton S, Luc Lai J, Preudhomme C, Lepelley P, Bauters F, et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. *Br J Haematol* 1997;98:983-91.
18. Hofmann WK, Heil G, Zander C, Wiebe S, Ottmann OG, Bergmann L, et al. Intensive chemotherapy with idarubicin, cytarabine, etoposide, and G-CSF priming in patients with advanced myelodysplastic syndrome and high-risk acute myeloid leukemia. *Ann Hematol* 2004;83:498-503.