Value of allogeneic *versus* autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomized European Intergroup Trial

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Citation: de Witte T, Hagemeijer A, Suciu S, Belhabri A, Delforge M, Kobbe G, Selleslag D, Schouten HC, Ferrant A, Biersack H, Amadori S, Muus P, Jansen JH, Hellström-Lindberg E, Kovacsovics T, Wijermans P, Ossenkoppele G, Gratwohl A, Marie J-P, and Willemze R. Value of allogeneic versus *autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomized European Intergroup Trial. Haematologica 2010;95(10):1754-1761. doi:10.3324/haematol.2009.019182*

Supplementary Appendix

Inclusion and exclusion criteria

The age of the patients was between 16 and 60 years, but some centers extended the age limit to 70 years depending on the policy of the center. Patients with blast crisis of chronic myeloid leukemia or with leukemias supervening after other myeloproliferative diseases were excluded from this study. Other exclusion criteria were: inadequate renal and liver function with creatinine and bilirubin values greater than 1.5 times the upper limit of normal, severe heart failure requiring diuretics or with an ejection fraction of less than 50%, and severe concomitant neurological disease. Patients with other progressive malignant diseases were also excluded from this study, but secondary acute leukemias following cured Hodgkin's disease or other malignancies were allowed, as were secondary leukemias following exposure to alkylating agents or radiation for any other reason.

Laboratory investigations

Apart from the other standard investigations it was mandatory to perform cytogenetic analysis with banding techniques prior to the start of chemotherapy. Metaphase and interphase FISH analyses were performed on sorted cell fractions, as described by Kroef *et al.*[1] Probes used in this study were Vysis LSI 7q D7S486 SO/CEP7 SG (for resp. 7q31 and centromere 7), Vysis LSI 5q ERG-1 SO/D5S23 SG (for resp. 5q31 and 5p15.2), D8Z2 (for centromere 8) and DYZ1 (for centromere Y).

Transplantation regimens

Two conditioning regimens for allogeneic stem cell transplantation (SCT) and autologous SCT were recommended. One regimen was cyclophosphamide 60 mg/kg/day on 2 consecutive days and total body irradiation (TBI) 12 Gy in four to six fractions over 2 or 3 days. The alternative regimen was busulphan 4 mg/kg/day on 4 consecutive days in combination with cyclophosphamide 60 mg/kg/day on 2 days. Prophylaxis of graft-*versus*-host disease (GVHD) following allogeneic SCT consisted of cyclosporine A alone or cyclosporine A in combination with methotrexate. T-cell depletion of the allograft was allowed according to the policy of the centers. The minimal required number for a successful harvest was 1×10^8/kg nucleated cells and 2×10^6 $CD34^+$ cells/kg (autologous peripheral blood SCT).

Definitions

The World Health Organization (WHO) classification was not available at the onset of the study. Therefore the French-American-British (FAB)-classification was used throughout the study, but we also classified the patients according to the percentage of marrow blasts, which allows a distinction between refractory anemia with excess blasts (RAEB)-1 and RAEB-2 according to the WHO-classification. Therapy-related myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) (tMDS/tAML) was defined as MDS or AML supervening after chemotherapy or radiotherapy for an earlier (non)-malignant disease.

Secondary AML (sAML) or transformed MDS was defined as AML after documented MDS lasting 6 months or longer. The Cancer and Leukemia Group B criteria for response to treatment and relapse were used.[2]

Stratification procedures

Randomization (autologous peripheral blood SCT *versus* high-dose cytarabine) was stratified for center, response to first induction cycles (complete response *versus* partial response) and cytogenetic risk groups [good prognosis: t(8;21), inv.16, del. 16, t(16;16] *versus* intermediate prognosis: only normal metaphases, single abnormality -Y or -X versus

poor prognosis: -5, 5q-, -7, 7q-, +8, complex *versus* all other single abnormalities *versus* technical failure *versus* not done) using a minimization technique. We used this cytogenetic stratification because the IPSS cytogenetic risk classification was published after the start of this study. For the analysis of the results we applied the IPSS cytogenetic classification. The main difference is the inclusion of trisomy 8 in the IPSS intermediate risk group (*Online Supplementary Table S1*).[3]

Details of allogeneic stem cell transplantation procedures

Bone marrow was the source of stem cells for 18 patients and peripheral blood stem cells mobilized after administration of granulocyte colony-stimulating factor were used in 29 patients. Forty-five out of 47 patients were treated with a marrow ablative conditioning regimen. This was a TBI-containing regimen in 26 patients and a busulphan-containing regimen in 19 patients (incomplete data for 2 patients). T-cell depletion was used in 18 patients.

References

1. Kroef MJ, Fibbe WE, Mout R, Jansen RP, Haak HL, Wessels JW, et al. Myeloid but not lymphoid cells carry the 5q deletion: polymerase chain reaction analysis of loss of heterozygosity using mini-repeat sequences on highly purified cell fractions. Blood. 1993;81(7):1849-54.
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3. 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(6):2079-88.

Online Supplementary Table S1. Patients' characteristics and their prognostic relevance regarding survival from registration in the Criant study.

Variable	Number of patients (%)	4-yr survival rate (SE%)	Hazard ratio (95% CI)	*P* value*
MDS	264 (77)	29 (3)	1.0	
AML-MDS	77 (23)	25 (5)	1.2 (0.9, 1.6)	0.27
Age (years)				(<0.0001)
≤ 45	103 (30)	43 (5)	1.0	
46-55	133 (39)	25 (4)	1.8 (1.3, 2.5)	0.0003
> 55	105 (31)	19 (4)	2.0 (1.4, 2.8)	0.0001
Duration of disease prior to treatment				(0.02)
< 6 months	286 (84)	30 (3)	1.0	
≤ 6 months	46 (13)	13 (5)	1.5 (1.1, 2.2)	0.009
White blood cell count (×10⁹/L)				(0.02)
< 2.5	117 (34)	25 (4)	1.0	
2.5 – 4.9	84 (25)	30 (5)	0.8 (0.6, 1.1)	0.15
5 – 24.9	103 (30)	35 (5)	0.8 (0.6, 1.0)	0.08
≥ 25	37 (11)	19 (6)	1.4 (0.9, 2.1)	0.13
Bone marrow blasts (%)				(0.4)
< 5	15 (4)	20 (10)	1.0	
5 - 9	33 (10)	42 (9)	0.6 (0.3, 1.1)	0.09
10-19	114 (33)	29 (4)	0.6 (0.3, 1.1)	0.09
20-29	84 (25)	28 (5)	0.7 (0.4, 1.2)	0.20
≥ 30	66 (19)	28 (6)	0.7 (0.4, 1.3)	0.29
Number of cytopenias				(0.02)
0-1	69 (20)	30 (6)	1.0	
2	131 (38)	35 (4)	0.9 (0.7, 1.3)	0.60
3	141 (41)	21 (4)	1.3 (1.0, 1.8)	0.09
IPSS risk groups (MDS patients)				(0.12)
Intermediate-1	22 (8)		1.0	
Intermediate-2	85 (32)		1.2 (0.7, 2.1)	0.58
High	111 (42)		1.6 (1.0, 2.8)	0.08
Missing	46 (17)		1.4 (0.7, 2.5)	0.33
Cytogenetic risk groups according to IPSS				(<0.0001)
Good	135 (40)	44 (4)	1.0	
Intermediate	65 (19)	27 (6)	1.4 (1.0, 2.0)	0.04
Poor	95 (28)	6 (3)	3.4 (2.5, 4.6)	<0.0001
Missing	46 (14)	29 (7)	1.4 (0.9, 2.1)	0.10
Cytogenetic risk groups according to IPSS, including FISH				(<0.0001)
Good	127 (37)	44 (4)	1.0	
Intermediate	63 (19)	28 (6)	1.4 (1.0, 2.1)	0.05
Poor	107 (31)	9 (3)	3.1 (2.3, 4.2)	<0.0001
Missing	44 (13)	30 (7)	1.4 (0.9, 2.0)	0.16

**: P value given by the Wald-test, corresponding to pairwise comparisons or the overall comparison, indicated between brackets.*