# Impact of genetic abnormalities after allogeneic stem cell transplantation in multiple myeloma: a report of the Société Française de Greffe de Moelle et de Thérapie Cellulaire

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## ABSTRACT

### Background

The impact of cytogenetic abnormalities in multiple myeloma after allogeneic stem cell transplantation has not been clearly defined. This study examines whether allogeneic stem cell transplantation could be of benefit for myeloma patients with high-risk cytogenetic abnormalities.

### Design and Methods

This is a retrospective multicenter analysis of the registry of the Société Française de Greffe de Moelle et de Thérapie Cellulaire, including 143 myeloma patients transplanted between 1999 and 2008.

### Results

The incidences of cytogenetic abnormalities were 59% for del(13q), 25% for t(4;14), 25% for del(17p) and 4% for t(14;16). When comparing the population carrying an abnormality to that without the same abnormality, no significant difference was found in progression-free survival, overall survival or progression rate. Patients were grouped according to the presence of any of the poor prognosis cytogenetic abnormalities t(4;14), del(17p) or t(14;16) (n=53) or their absence (n=32). No difference in outcomes was observed between these two groups: the 3-year progression-free survival, overall survival and progression rates were 30% *versus* 17% ($P$=0.9), 45% *versus* 39% ($P$=0.8) and 53% *versus* 75% ($P$=0.9), respectively.

### Conclusions

These data indicate that allogeneic stem cell transplantation could potentially be of benefit to high-risk myeloma patients.

Key words: multiple myeloma, cytogenetic abnormalities, allogeneic transplantation.

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## Introduction

Multiple myeloma (MM) is a clonal disorder of malignant plasma cells. A number of cytogenetic abnormalities (CA) in the malignant plasma cell clone have been described, including deletions of chromosome 13 or chromosome 17, and translocations involving the immunoglobulin heavy chain.[1]

Optimal treatment for MM is still poorly defined, and despite recent progress this remains an incurable disease. Nevertheless, patients' outcomes are clearly heterogeneous, with survival ranging from a few months to several years. Because of the move towards individualized therapy, prognostic risk stratifications have been proposed based on biological markers[2] or chromosomal abnormalities.[3,4] Thus, del(13q), del(17p) and t(4;14) have been recognized as strong risk factors, carrying poor prognosis in patients treated with conventional chemotherapy or autologous stem cell transplantation (auto-SCT).[5,6] Over the past few years, there have been many important changes in the therapy for MM with the development of novel therapeutic strategies, such as the new agents, bortezomib and lenalidomide, which have shown promising results in terms of overall response rates and survival outcomes. It has even been suggested that the use of these novel agents could overcome the negative impact of del(13q) and t(4;14); however, these agents do not seem to provide an advantage to patients with del(17p) who still exhibit the worse outcomes.[7-12]

The role of allogeneic stem cell transplantation (allo-SCT) in MM remains a matter of controversy. To better evaluate its benefits as first-line therapy, seven prospective studies have been conducted or are currently ongoing comparing single or double auto-SCT to a tandem approach, defined as reduced intensity conditioning (RIC) transplants following a first auto-SCT.[13-18] The published results, however, have been the subject of intensive debate and did not lead to a strong consensus for a first-line therapy in MM.[19]

Some have also questioned whether allo-SCT could benefit patients with high-risk chromosomal abnormalities. Unfortunately, prospective studies have so far failed to answer this question due to the small numbers of patients carrying poor prognostic abnormalities in these trials. Only the retrospective study of 101 patients conducted in 2008 by Schilling *et al.* carried out an exhaustive investigation into the impact of genetic abnormalities in allo-SCT for MM.[20] The data suggest that allo-SCT can overcome the negative impact of t(4;14) but does not benefit del(17p) patients who still have poor outcomes. Additional data on cytogenetics in the context of allo-SCT are clearly needed. Therefore, we carried out a retrospective study in a cohort of 143 MM patients who underwent allo-SCT to evaluate the prognostic impact of several genetic abnormalities, i.e. [del(13q), t(4;14), del(17p), t(11;14) and t(14;16)], detected by fluorescent *in situ* hybridization (FISH).

## Design and Methods

### Study design

This study is a retrospective multicenter analysis using the registry of the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) and the files of the cytogenetic laboratories from the Intergroupe Français du Myélome (IFM) and the Myélome Autogreffe Groupe (MAG). To be included in the study, MM patients had to have received allo-SCT and to have undergone a cytogenetic study of at least two of the three major abnormalities, i.e. del(13q), t(4;14) and del(17p). Among 520 patients who had received allo-SCT from May 1984 to February 2008, 210 underwent cytogenetic analysis but only 143 were analyzed for two or more of the previously mentioned chromosomal abnormalities. These patients had been transplanted in 23 different French centers between February 1999 and February 2008. All SFGM-TC centers report a minimum essential data set. Additional questionnaires were sent to the referring physicians to obtain missing data. The study was approved by the scientific committee of the SFGM-TC and carried out in accordance with the SFGM-TC guidelines.

### Cytogenetic analysis

Chromosomal abnormalities were analyzed by interphase FISH on purified bone marrow plasma cells, as previously described.[21] FISH analyses were performed either at diagnosis or relapse before allo-SCT, except for 3 patients for whom the analyses were performed after allo-SCT. Patients included in our study were analyzed for the following cytogenetic abnormalities: del(13q), t(4;14), del(17p), t(11;14) and t(14;16); however, analysis of each of these abnormalities was not performed on all patients due to the small quantities of purified plasma cells.

### Definitions

Response to treatment, relapse, and progression were defined according to the criteria of the European Group for Blood and Marrow Transplantation[22] and the International Myeloma Working Group.[23] Complete remission (CR) was defined as the absence of detectable monoclonal component in serum and urine by immunofixation and fewer than 5% bone marrow plasma cells; however, bone marrow evaluation was not systematically performed in some centers. Very good partial response (VGPR) was defined as a 90% decrease in the blood monoclonal component level and a urine monoclonal component lower than 100 mg/24 h. Partial response (PR) was defined as a 50% decrease in the serum monoclonal component or a 90% decrease in the urine monoclonal component. We considered patients to have a chemosensitive disease when they were in CR, VGPR or PR at the time of allo-SCT. On the contrary, patients were considered to be refractory when their disease was either stable or progressive at the time of transplant. Standard criteria were used for graft-*versus*-host-disease (GvHD) assessment.[24,25] Chronic GvHD was documented only for patients surviving more than 100 days. Progression-free survival (PFS) and overall survival (OS) were measured in months and calculated from the date of allo-SCT until the respective events.

### Statistical analyses

Survival functions were estimated using the Kaplan-Meier method. Univariate survival analyses were performed using log rank tests for qualitative variables and univariate Cox's models for quantitative and time-dependant variables. All prognostic factors found to be significant at a level of $P$ lower than 0.05 in the univariate analyses were included into stepwise regression models using Cox's proportional hazards models. The following factors were included in the univariate analyses: patient sex, disease stage, beta-2 microglobulin, number of prior auto-SCT, number of prior lines of therapy, use of thalidomide or bortezomib in prior treatments, disease status at transplant, interval from diagnosis to transplant, stem cell source, donor type, conditioning regimen, use of ATG, age at transplant, post-transplant response, acute and chronic GvHD, and cytogenetic groups. All tests were two-sided and significance levels were set at 0.05. A 95% confidence interval

(CI) was used. Statistical analysis was performed using the SAS V9 statistical package (SAS Institute, Cary, NC, USA).

## Results

### Patients' characteristics

One hundred and forty-three myeloma patients were included in the present study; their main characteristics are summarized in Table 1. Briefly, the median age of the study population was 51 years (range 29-62 years). The median time from diagnosis to transplantation was 16 months (range 4-175 months). The median number of lines of therapy before allo-SCT was 2. Forty-eight patients received allo-SCT as part of first-line therapy: 19 after a myeloablative conditioning regimen and 29 in a planned tandem auto/RIC allo-SCT program. Ninety-two received allo-SCT beyond first-line treatment: 55 were in second-line treatment and 27 in third-line treatment or more. Among them, all had received at least one prior auto-SCT. Thirty-eight and 33 patients received bortezomib or thalidomide, respectively, as part of their prior lines of therapy. Eighty-four percent of patients had chemosensitive disease at the time of allo-SCT. RIC regimens were used in 77% of transplantations, with inclusion of ATG in 48% of these cases. The source of stem cells was peripheral blood in 110 patients (77%) and bone marrow in 29 patients (20%). Sixty-eight percent of donors were matched-related.

### Cytogenetic abnormalities

All patients but 2 were screened for 13q deletions. The t(4;14), del(17p), t(11;14) and t(14;16) cytogenetic abnormalities were tested in 123 (86%), 95 (66%), 97 (68%) and 104 (73%) patients, respectively. Seventy-two percent of patients were screened for four or more chromosomal abnormalities. Chromosomal abnormalities were detected in 106 of 143 patients (74%), distributed as follows (in percent of patients evaluable for each abnormality): 59% for del(13q), 25% for t(4;14), 25% for del(17p), 24% for t(11;14) and 4% for t(14;16) (*Online Supplementary Table S1*). Twenty-eight (87.5%) of the t(4;14) positive patients and 14 (56%) of the del(17p) positive patients also had the del(13q) abnormality. Among the 31 t(4;14) patients, 4 were also positive for del(17p) and one for t(14;16). Finally, one patient had del(17p) and t(14;16).

Patients' disease and treatment courses in each cytogenetic group were not strictly comparable (Table 2). Indeed, the del(13q) population received significantly less prior lines of treatment ($P$=0.0001) and less thalidomide ($P$=0.02) or bortezomib ($P$=0.02) than the non-del(13q) group. The proportion of patients receiving a conditioning regimen including ATG was greater in the del(13q) population ($P$=0.01), in part because a number of these del(13q) patients were included in the prospective IFM 99-03 trial where the first-line therapy was a reduced intensity conditioning allo-SCT with ATG.[13] Lastly, patients with del(17p) underwent significantly more auto-SCT prior to allo-SCT than patients without del(17p) ($P$=0.03) and were less often transplanted in the first year of diagnosis ($P$=0.02).

### Post-transplant outcomes

Post-transplant responses are summarized in the *Online Supplementary Table S2*. Nine patients (6%) were not evaluable because of early deaths. Overall, 53% of evaluable patients reached at least VGPR after allo-SCT compared to 19% before transplant. The median follow up of the survivors was 34 months (range 3-111 months). Three-year PFS, OS and progression rate were 33%, 53% and 53%, respectively. Treatment-related mortality (TRM) was 25% at two years. Acute GvHD occurred in 66 patients (47%) with 44 patients (32%) having grade II to IV. Chronic GvHD, evaluable in 123 patients surviving beyond day 100, occurred in 53 patients (43%), and was limited in 22 patients (18%) but extensive in 31 (25%). Chronic GvHD was associated with better PFS ($P$=0.0001, HR=1.8-5.1).

Moreover, the population of MM patients who underwent allo-SCT but were not analyzed in our study because of missing cytogenetic data (*see above*) showed similar post-transplant outcomes to our study population: 28% *versus* 33% ($P$=0.12), 50% *versus* 53% ($P$=0.19), 55% *versus* 53% ($P$=0.18) for 3-year PFS, OS and progression rate, respectively.

**Table 1.** Patients' characteristics.

| | N. (%)* |
|---|---|
| **Total** | **143** |
| Median age, years (range) | 51 (29-62) |
| Sex, n. male | 85 (59) |
| Stage (Salmon and Durie) at diagnosis | |
| I / II | 27 (19) |
| III | 115 (81) |
| β2 microglobulin (mg/L) at diagnosis | |
| > 4 | 58 (51) |
| Number of prior treatments | |
| 1 | 48 (37) |
| 2 | 55 (42) |
| > 2 | 27 (21) |
| Including bortezomib / thalidomide | 38 (29) / 33 (25) |
| Number of prior auto-SCT | |
| 0 | 19 (13) |
| 1 | 106 (74) |
| > 1 | 18 (13) |
| Disease status at transplant | |
| Complete remission + very good partial response | 27 (19) |
| Partial response | 92 (65) |
| Stable disease + progressive disease | 23 (16) |
| Median time from diagnosis to transplant, months (range) | 16 (4-175) |
| Delay diagnosis-transplant < 1 year | 56 (39) |
| Conditioning regimens | |
| Myeloablative | 32 (23) |
| Reduced intensity | 108 (77) |
| Antithymoglobulin | 68 (48) |
| Donor | |
| Identical sibling | 97 (68) |
| Unrelated | 46 (32) |
| Matched | 34 (24) |
| Mismatched | 12 (8) |
| Cell source | |
| Bone marrow | 29 (20) |
| Peripheral blood stem cells | 110 (77) |
| Cord blood | 4 (3) |

** Expressed as percent of available data.*

### Impact of cytogenetic abnormalities

The post-transplant response was analyzed for each cytogenetic abnormality. The response rate of patients who achieved at least VGPR after allo-SCT was 50% in del(17p), 60% in t(4;14), 59% in del(13q), and 43% in t(11;14) patients. There was no significant difference in post-transplant response between patients carrying cytogenetic abnormalities and those who did not. Moreover, there was no difference in 3-year PFS, OS, and relapse rate and 2-year TRM between patients with or without each specific cytogenetic abnormality (Table 3 and *Online Supplementary Figure S1*). The number of patients carrying t(14;16) was too small to analyze this subgroup of cases.

In order to study the impact of high-risk cytogenetics, we then defined two groups of patients, a high and a non-high risk group. The high-risk group (n=53) included patients with either t(4;14) (n=26), del(17p) (n=19) or t(14;16) (n=2), and patients carrying 2 of these 3 cytogenetic abnormalities at the same time (n=6) (4 t(4;14) patients with del(17p), one t(4;14) with t(14;16) and one del(17p) with t(14;16); *see above*). The non-high risk group (n=32) included patients without any of these 3 poor-risk abnormalities, among patients screened specifically for them. Both groups were comparable in terms of patients' characteristics at time of diagnosis and allo-SCT. Strikingly, we did not observe any difference in outcomes between these two groups. The 3-year PFS, OS and progression for the high and non-high risk groups were 30% *versus* 17% ($P$=0.9), 45% *versus* 39% ($P$=0.8) and 53% *versus* 75% ($P$=0.9), respectively (Figure 1).

### Univariate and multivariate analyses of other prognostic factors

Prognostic risk factors associated with better PFS, OS or progression in univariate and multivariate analyses are shown in Tables 4 and 5. In univariate analysis, better PFS was associated with age at transplant (as a continuous variable, $P$=0.03), sensitive disease at transplant ($P$=0.04), time from diagnosis to allo-SCT less than one year ($P$=0.06), two or less prior modes of treatment ($P$=0.001), achievement of at least VGPR after allo-SCT ($P$=0.0002) and the occurrence of chronic GvHD ($P$=0.0001) (Table 4). On the contrary, a worse 3-year PFS was significantly associated with treatment with thalidomide or bortezomib ($P$=0.01), which were mostly used in MM patients who underwent allo-SCT late in the course of their disease (92% had two or more prior modes of treatment and only 14% underwent allo-SCT in the first year after diagnosis). In multivariate analysis, the risk factors that remained associated with a better 3-year PFS were the number of prior modes of treatment ($P$=0.002, HR=0.29; CI 95% 0.15-0.56), age at transplant ($P$=0.01, HR=1.1; CI 95% 1.01-1.18), achievement of at least VGPR after allo-SCT ($P$=0.02, HR=2.01; CI 95% 1.11-3.62) and the occur-

**Table 2.** Main characteristics of patients at time of allo-SCT according to cytogenetic abnormalities.

| | Del(13q) *vs.* no del(13q) | | | t(4;14) *vs.* no t(4;14) | | | Del(17p) *vs.* no del(17p) | | | t(11;14) *vs.* no t(11;14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Del(13q) n=84 n (%) | No del(13q) n=57 n (%) | *P* | t(4;14) n=31 n (%) | No t(4;14) n=92 n (%) | *P* | Del(17p) n=24 n (%) | No del(17p) n=71 n (%) | *P* | t(11;14) n=24 n (%) | No t(11;14) n=73 n (%) | *P* |
| Median age at transplant (years) | 51 | 49.3 | NS | 49.5 | 50.9 | NS | 54 | 48.7 | NS | 51.9 | 50.1 | NS |
| β2 microglobulin > 4 mg/L at diagnosis | 34 (50) | 22 (51) | 0.72 | 14 (56) | 35 (49) | 0.34 | 10 (55) | 32 (52) | 0.34 | 7 (41) | 32 (51) | 0.39 |
| Number of prior treatments | | | | | | | | | | | | |
| < 2 | 38 (50) | 9 (17) | 0.0001 | 14 (48) | 28 (33) | 0.15 | 5 (22) | 23 (35) | 0.27 | 9 (40) | 30 (44) | 0.8 |
| Including bortezomib | 16 (21) | 21 (39) | 0.02 | 10 (34) | 18 (21) | 0.16 | 10 (45) | 26 (40) | 0.65 | 4 (18) | 14 (20) | 0.8 |
| Including thalidomide | 14 (18) | 19 (35) | 0.02 | 8 (27) | 23 (27) | 0.98 | 7 (32) | 16 (25) | 0.5 | 7 (31) | 16 (23) | 0.43 |
| Number of prior transplantations ≥ 2 | 8 (9.5) | 10 (17.5) | 0.16 | 3 (10) | 15 (16) | 0.36 | 6 (25) | 6 (11) | 0.03 | 3 (12.5) | 12 (16) | 0.64 |
| Disease status at transplant | | | | | | | | | | | | |
| CR+VGPR+PR | 69 (83) | 46 (82) | 0.87 | 24 (80) | 76 (82) | 0.74 | 18 (75) | 60 (86) | 0.17 | 22 (91) | 58 (80) | 0.2 |
| Delay diagnosis-transplant < 1 year | 39 (47) | 19 (33) | 0.1 | 15 (50) | 36 (39) | 0.3 | 5 (20) | 34 (48) | 0.02 | 9 (37.5) | 33 (46) | 0.5 |
| ATG in conditioning regimen | 47 (57) | 20 (35) | 0.01 | 15 (48) | 44 (49) | 0.9 | 10 (41) | 35 (50) | 0.48 | 14 (58) | 39 (53) | 0.67 |

*CR: complete remission; VGPR: very good partial response; PR: partial response; SD, stable disease; PD: progressive disease; ATG: antithymoglobulin.*

**Table 3.** Univariate analysis of responses, PFS, OS and progression after allo-SCT according to cytogenetic abnormalities.

| | Del(13q) | Del(13q) *vs.* no del(13q) | | t(4;14) *vs.* no t(4;14) | | | Del(17p) *vs.* no del(17p) | | | t(11;14) *vs.* no t(11;14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Del(13q) n=84 | No del(13q) n=57 | *P* | t(4;14) n=31 | No t(4;14) n=92 | *P* | Del(17p) n=24 | No del(17p) n=71 | *P* | t(11;14) n=24 | No t(11;14) n=73 | *P* |
| CR+VGPR (%) | 59 | 50 | 0.17 | 60 | 54 | 0.23 | 50 | 51 | 0.83 | 43 | 52 | 0.11 |
| 3-year PFS (%) | 38 | 25 | 0.18 | 26 | 33 | 0.5 | 27 | 22 | 0.66 | 25 | 31 | 0.45 |
| 3-year OS (%) | 54 | 52 | 0.76 | 39 | 52 | 0.21 | 34 | 42 | 0.35 | 43 | 50 | 0.62 |
| 3-year progression (%) | 49 | 62 | 0.42 | 55 | 56 | 0.67 | 45 | 69 | 0.9 | 65 | 56 | 0.43 |
| 2-year TRM (%) | 20 | 28 | 0.27 | 29 | 24 | 0.36 | 38 | 22 | 0.15 | 23 | 27 | 0.58 |

*CR: complete remission; PFS: progression-free survival; OS: overall survival; TRM: transplantation-related mortality; VGPR: very good partial response.*

rence of chronic GvHD (*P*=0.001, HR=0.29; CI 95% 0.16-0.52). The number of prior modes of treatment was also associated with better OS and progression rate, and achievement of at least VGPR after allo-SCT was associated with progression in multivariate analysis (Table 5). Achieving at least VGPR after allo-SCT remained a significant prognostic factor of outcome for all cytogenetic groups. Strikingly, in the del(17p) population, the 3-year PFS, OS and progression rates after allo-SCT were 71%, 69% and 17%, respectively, in patients who achieved at least VGPR, compared with 0%, 0% and 100% in those del(17p) patients who did not achieve VGPR.

## Discussion

Allo-SCT has been recognized as a potential therapeutic

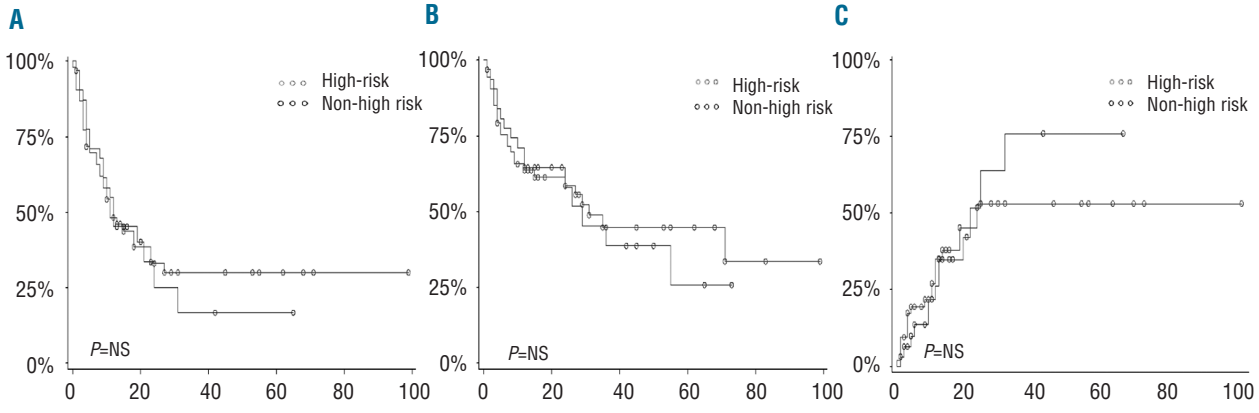


**Figure 1.** (A) Progression-free survival, (B) overall survival, and (C) progression rate in 'high-risk' (red) and 'non-high risk' (black) groups.

**Table 4.** Univariate analysis of main prognostic factors at three years after allo-SCT.

| Prognostic factors | 3-year PFS, % (CI) | *P* | 3-year OS, % (CI) | *P* | 3-year progression, % (CI) | *P* |
|---|---|---|---|---|---|---|
| Age at transplant (continuous variable) | - | 0.004 | - | 0.03 | - | NS |
| β2 microglobulin (mg/L) | | | | | | |
| < 4 | 42 (3.7) | NS | 54 (3.5) | NS | 42 (1.5) | NS |
| ≥ 4 | 25 (2.1) | | 52 (3.1) | | 64 (1.5) | |
| Number of prior treatments | | | | | | |
| 1 or 2 | 36 (2.5) | 0.01 | 58 (3.0) | 0.01 | 52 (1.0) | 0.006 |
| > 2 | 20 (5.0) | | 27 (2.5) | | 60 (6.0) | |
| Prior treatments including | | | | | | |
| Bortezomib | 0 (1.8) | 0.01 | 53 (2.0) | NS | 100 (2.2) | 0.08 |
| No bortezomib | 38 (2.9) | | 56 (3.1) | | 50 (3.2) | |
| Thalidomide | 12 (1.8) | 0.01 | 36 (2.2) | NS | 80 (2.1) | 0.02 |
| No thalidomide | 39 (2.9) | | 57 (3.1) | | 47 (3.2) | |
| Number of prior transplantations | | | | | | |
| < 2 | 33 (2.5) | NS | 53 (2.8) | NS | 55 (2.9) | NS |
| ≥ 2 | 31 (2.2) | | 48 (2.8) | | 55 (2.3) | |
| Disease status at transplant | | | | | | |
| Responders | 39 (2.3) | 0.04 | 53 (2.9) | NS | 47 (1.1) | 0.04 |
| Non-responders | 33 (5.7) | | 45 (3.7) | | 54 (7.1) | |
| Time from diagnosis to transplant | | | | | | |
| < 12 months | 37 (3.6) | 0.06 | 58 (3.9) | NS | 52 (3.9) | NS |
| > 12 months | 28 (1.8) | | 47 (1.8) | | 56 (1.3) | |
| Conditioning regimens | | | | | | |
| Myeloablative | 35 (2.6) | NS | 52 (3.0) | NS | 51 (2.1) | NS |
| Reduced intensity | 32 (2.1) | | 51 (2.0) | | 57 (3.2) | |
| Antithymoglobulin | 32 (2.6) | NS | 51 (3.8) | NS | 57 (1.4) | NS |
| No antithymoglobulin | 32 (3.3) | | 55 (3.1) | | 53 (4.0) | |
| Post-transplant response | | | | | | |
| CR+VGPR | 51 (3.5) | 0.0002 | 64 (4.0) | 0.02 | 41 (1.2) | 0.001 |
| < VGPR | 23 (2.9) | | 43 (3.3) | | 68 (1.7) | |

*CI: confidence interval; CR: complete remission; NS: not significant; PFS: progression-free survival; OS: overall survival; VGPR: very good partial response.*

**Table 5.** Multivariate analysis evaluating prognostic factors on 3-year PFS, OS and progression.

| | Progression-free survival | | Overall survival | | Progression | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age at transplant | 1.10 (1.01-1.18) | 0.01 | Not retained | | Not retained | |
| Sensitive disease at transplant | Not retained | | Not retained | | 0.35 (0.15-0.84) | 0.02 |
| Number of prior treatments | 0.29 (0.15-0.56) | 0.0002 | 0.43 (0.21-0.87) | 0.01 | 0.27 (0.13-0.57) | 0.002 |
| Chronic GvHD | 0.29 (0.16-0.52) | 0.0001 | Not retained | | Not retained | |
| Achievement of at least VGPR | 2.01 (1.11-3.62) | 0.02 | Not retained | | 2.81 (1.44-5.46) | 0.002 |

*CI: confidence interval; GvHD: graft-*versus*-host disease; VGPR: very good partial response.*

option in MM, especially since the introduction of RIC regimens and the use of a tandem transplantation approach, i.e. auto-SCT followed by RIC allo-SCT, has shown promise by reducing the TRM and inducing high CR rates.[26,27] Nevertheless, long-term control of the disease remains a key issue, even in patients treated first by RIC allo-SCT.[13-14,28] In our retrospective study, analysis of the whole population showed that the outcomes were slightly lower than the ones usually observed in prospective trials,[13-15,28] probably because it included many patients in relapse as well as patients with high-risk cytogenetic abnormalities. Our results were consistent with those reported in a large retrospective study of the EBMT registry.[29] The main prognostic factors identified in our study also agreed with those reported in the literature,[28-31] as patients not heavily pre-treated and with chemosensitive disease showed the best outcomes. Moreover, achievement of at least VGPR after allo-SCT was also identified as an important factor associated with prolonged PFS and OS, in agreement with what has been recently described after auto-SCT[32] and first-line RIC allo-SCT.[28]

The impact of cytogenetic abnormalities has been widely studied after conventional therapies and auto-SCT,[6] and conclusive data are lacking in the setting of allo-SCT. The present study was undertaken to determine whether allo-SCT could be of benefit to patients with particular cytogenetic abnormalities. It is a comprehensive analysis with 72% of patients having been screened for at least four cytogenetic abnormalities. The incidences of high-risk cytogenetic abnormalities, i.e. del(13q), t(4;14), and del(17p), were higher in our cohort than those usually reported in patients treated in prospective studies,[1,4,6,33-34] reflecting the fact that these poor-prognosis patients are more frequently programmed to undergo allo-SCT.

Firstly, we did not find any significant difference in outcomes between t(4;14) and non-t(4;14) patients. This observation, which has also been reported by Schilling *et al.*,[20] suggests that allo-SCT could overcome the poor prognosis of t(4;14) usually observed after conventional therapies and auto-SCT. As recent studies suggest that bortezomib and lenalidomide can overcome the negative prognosis of t(4;14) myeloma,[8-10,12,35] it might be interesting to evaluate allo-SCT in the context of novel therapies in this group of patients.

The del(17p) patients in our study were heavily pretreated, which probably explains the high TRM observed in this population; 38% at two years. Indeed, 78% had received at least 2 prior lines of treatment and 25% had at least 2 prior auto-SCT. However, it is worth noting that these patients showed a 3-year progression rate which did not exceed 45%, which is quite encouraging for this high-risk population (Table 3). Taken together, this raises the question of whether allo-SCT performed early in the course of the disease would benefit the del(17p) population of patients who usually experience poor outcomes after conventional therapies[36,37] and seem to be relatively resistant to novel agents.[7,8,12,35] Interestingly, this question will be addressed in a future phase II prospective trial to be conducted by the French IFM group in which newly diagnosed del(17p) patients will receive a first-line allo-SCT.

Regarding the del(13q) and t(11;14) populations, our study did not show that these abnormalities had any impact on outcomes. This is not surprising for the t(11;14), as most studies found a neutral prognosis for this cytogenetic group.[6,38] The del(13q) was the first chromosomal abnormality found to be associated with shortened survival. Some studies found a small difference in outcome between del(13q) and non-del (13q) patients after auto-SCT.[39,40] In our study, no difference in outcome was observed between these two patient populations, suggesting a possible advantage of allo-SCT in del(13q) patients. Recent findings suggest that del(13q) is no longer an independent risk factor, as it is often associated with other cytogenetic abnormalities, e.g. t(4;14) and del(17p)).[6,20] Unfortunately, the number of patients with only the del(13q) abnormality was too low in our study (n=8) to demonstrate any significant impact on outcomes.

As the comparison of patients with and without a specific cytogenetic abnormality can be flawed by the unknown presence of other cytogenetic abnormalities in some patients, we created a high-risk group and a non-high risk group (Figure 1). There was no difference in outcomes between these two groups. These data indicate that the negative impact of high-risk cytogenetic abnormalities could be compensated by allo-SCT.

The retrospective nature of the analysis and the heterogeneity of patients in the study can be considered limitations. Moreover, it is possible that some bias was introduced because the study did not include patients with particularly aggressive disease as they did not survive long enough to be referred to allo-SCT. Nevertheless, we believe that the study offers new information about the prognostic impact of high-risk cytogenetic abnormalities in the setting of allo-SCT, which has not been extensively studied previously.

In summary, our data show that the high-risk cytogenetic abnormalities studied, in particular t(4;14) and del(17p), had no impact on outcomes, suggesting a potential benefit of allo-SCT in these populations. Furthermore, they indicate for the first time that allo-SCT can offset the negative prognosis of del(17p) patients. Prospective studies are thus clearly warranted

to better define the role of allo-SCT for these high-risk patients, either defined by cytogenetic abnormality or other newly identified prognostic markers, including genome expression profiles.[41,42] The role of allo-SCT also needs to be re-evaluated in the context of novel therapeutic agents, considering the advantageous effects on outcome observed with these drugs. Ideally this should ideally be done via clinical trials.

## Authorship and Disclosures

*The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.*

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