Long-term follow up of a comparison of non-myeloablative allografting with autografting for newly diagnosed myeloma

Short title: Allografting in myeloma: long-term follow up

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ABSTRACT

Before the introduction of new drugs, we designed a trial where treatment of newly diagnosed myeloma patients was based on the presence or absence of HLA-identical siblings. First-line treatments included a cytoreductive autograft followed by a non-myeloablative allograft or a second melphalan-based autograft. Here, we report long-term clinical outcomes and discuss them in the light of the recent remarkable advancements in the treatment of myeloma. After a median follow up of 7 years, median overall survival (OS) was not reached (p=0.001) and event-free survival (EFS) was 2.8 years (p=0.005) for 80 patients with HLA-identical siblings and 4.25 and 2.4 years for 82 without, respectively. Median OS was not reached (p=0.02) and EFS was 39 months (p=0.02) in the 58 patients who received a non-myeloablative allograft whereas OS was 5.3 years and EFS 33 months in the 46 who received two high-dose melphalan autografts. Among patients who reached complete remission in these 2 cohorts, 53% and 19% are in continuous complete remission. Among relapsed patients rescued with “new drugs”, median OS from the start of salvage therapy was not reached and was 1.7 (p=0.01) years, respectively. Allografting conferred a long-term survival and disease-free advantage over standard autografting in this comparative study.
INTRODUCTION

Autologous transplantation has been regarded as the standard of care for young myeloma patients.\(^1\) Recently, “new drugs” such as lenalidomide and bortezomib have prolonged survival.\(^2,3\) Allografting has been considered the only potential cure.\(^4\) However, the high transplant-related mortality (TRM) has limited its use.\(^5,6\) After the observation that donor engraftment could be obtained after reduced intensity purine analog-based or non-myeloablative low-dose total body irradiation (TBI)-based conditionings, allografting has become more feasible with acceptable toxicity.\(^7-9\) Combining an autograft with a non-myeloablative conditioning and an allograft has lowered TRM to approximately 15% in myeloma.\(^10,11\) However, role and timing of allografting remain to be determined and convincing evidence that an allograft should routinely be performed is lacking.

We report the long-term results of a trial, designed before the introduction of “new drugs”, where the treatment assignment of newly diagnosed patients under the age of 66 was based on the presence or absence of an HLA-identical sibling (ClinicalTrials.gov number, NCT00415987).\(^12\)

METHODS

Patients and Treatments

Two-hundred-forty-five patients were consecutively diagnosed with stage IIA-IIIB myeloma from September 1998 to July 2004 at five Italian Centers. One-hundred-sixty-six of 199 with at least one sibling were HLA-typed to search for a potential sibling donor. Written informed consent was obtained from all patients. The study was approved by the five Institutional Review Boards according to the Declaration of Helsinki. A first report of this trial was previously published.\(^12\)
Patients eligible for chemotherapy received 2-3 courses of vincristine, adriamycin, and -dexamethasone-(VAD) based regimens. G-CSF-mobilized peripheral blood stem cells (PBSC) were collected after cyclophosphamide. Patients with HLA-identical siblings were offered the preceding induction followed by a standard autograft after melphalan, 200 mg/m\textsuperscript{2}, and, 2-4 months later, by an allograft with PBSC after non-myeloablative TBI (200 cGy). No maintenance/consolidation therapies were allowed. Patients without HLA-identical siblings were assigned to double autologous transplantation after intermediate- dose (100 mg/m\textsuperscript{2}) or high-dose (140-200 mg/m\textsuperscript{2}) melphalan (Figure 1).

Clinical outcomes were compared between patients with and without HLA-identical siblings and between the two patient cohorts who received the allograft and the two high-dose melphalan autografts. 12

**Response Criteria**

Complete remission (CR) required undetectable serum monoclonal immunoglobulins or urine light chains by electrophoresis and no monoclonal bands on immunofixation; less than 1% marrow plasma cells, and no increase in size or number of osteolytic lesions. Partial remission (PR) was defined as >75% reduction of the serum monoclonal immunoglobulin, at least 90% reduction in 24-hour urinary light chain excretion, no increase in size or number of osteolytic lesions or increase in marrow plasma cells. Patients with less than a PR after induction or autografting were considered refractory; the disease was considered stable if neither CR or PR was observed after allografting. Progressive disease was defined as a >25% increase in serum monoclonal immunoglobulin or urine light chains in patients with refractory or stable disease; relapse as the reappearance of marrow plasma cells, serum monoclonal immunoglobulins,
urinary light chains or new bone lesions in patients in CR, or a 25% increase in any disease marker for patients in PR.

**Statistical analysis**

Primary endpoints were overall (OS) and event-free survivals (EFS) from diagnosis by the intention-to-treat principle. Secondary endpoints included OS and EFS, disease response and TRM in patients who completed the assigned procedures. Survivals were calculated by the Kaplan-Meier method from diagnosis until death from any cause for OS, and from diagnosis until progression, relapse or death from any cause for EFS. OS was also evaluated from the start of salvage therapy after the allograft or the second high-dose autograft. Incidences of TRM, acute GVHD and chronic limited or extensive GvHD, of being on immunosuppression (IS) after developing chronic GVHD, and of dying while on IS were calculated by the cumulative incidence method by Gooley et al.\textsuperscript{13} Death without chronic GVHD was considered a competing risk for chronic GVHD; getting off IS was considered a competing risk for dying while on IS; and dying while on IS was considered a competing risk for getting off IS. Deaths due to non-relapse causes, except for non-hematological malignancies, were regarded as TRM. Proportions between groups were compared with Fisher’s exact test. Differences in OS and EFS were estimated with the Cox proportional hazards model. All P-values from regression models were derived from the log-rank test. Following the allograft or the second autograft, the probability that a patient was alive in the original CR and PR, or in a subsequent remission after salvage treatment, was estimated via an extension of the method described by Couper et al., allowing for multiple transitions between remission and relapse states.\textsuperscript{14} Multivariate models included presence or absence of an HLA-identical, sibling age, gender, myeloma protein isotype,
Durie\&Salmon stage, disease response at the first autograft. SAS 8.2 statistical software (SAS Institute, Cary, NC) and R 2.1.0, package “cmprsk” were used.

**RESULTS**

**Treatment assignment**

Patient characteristics are reported in Table 1. Prognostic factors were evenly distributed in all subgroups.\(^\text{12}\) Of the 162 HLA-typed patients, 80 had at least one potential HLA-identical donor and 60 of them were enrolled in non-myeloablative allograft program. Fifteen (18\%) who refused because of concerns about TRM and 5 (6\%) who had ineligible donors were included in the intention-to-treat analysis. Fifty-eight of the 60 (97\%) completed their assigned treatment. Of the 82 without donors, 59 were enrolled in the double high-dose melphalan autograft and 46 (78\%) completed the planned treatment. The remaining patients were either ineligible for chemotherapy or received reduced doses of melphalan.

**Long-term transplant-related toxicity and mortality**

*Non-myeloablative allografts* Grade II-IV acute GvHD developed in 40\% (23/58) of the patients.\(^\text{12}\) Of 55 patients, limited and extensive chronic GvHD developed in 9 (16\%) and in 32 at a median of 199 (range 100-441) and 199 (range 84-1192) days.

After a median follow up of 7.3 (range 5.4 – 10.4+) years from diagnosis and 6.5 (range 4.2 – 9.4+) years from the non-myeloablative allograft, 24 out of 58 (41\%) patients died: 13 (22\%) from disease progression, 9 (16\%) from TRM and 2 (3\%) from lung cancer. TRM was mainly due to complications associated with acute GvHD and chronic GvHD. Four patients in CR died of TRM.
High-dose melphalan autografts Overall, 13 (22%) of the 59 patients did not complete the assigned treatment because of disease progression (n.4), disease-related renal failure (n.3), TRM (n.1), consent withdrawal (n.3), and poor PBSC mobilization (n.2).

After a median follow up of 7.4 (range 5.6 – 10.7+) years from diagnosis and 6.2 (range 4.7 – 9.1+) years from the second autograft, 30 (65%) of the 46 patients died: 26 (56%) from disease progression, 1 (2%) from TRM (invasive aspergillosis), 1 (2%) from gall bladder cancer and 2 (4%) of complications during salvage treatments.

Disease response

Non-myeloablative allografts At the time of allografting, 8 of the 58 (14 %) patients were in CR and 36 (62 %) in PR giving an overall response (CR+PR) of 76%. Thirty-two of the 58 (55%) achieved CR at a median time of 5 months after the non-myeloablative allograft (range 0-35) and 18 (31%) PR, for an overall response rate of 86%. One additional patient, after obtaining an initial PR achieved CR after subsequent salvage therapy. The achievement of CR was not associated with the development of chronic GvHD (p=1). Twelve of the 32 patients in CR (37%) and 9 of the 18 in PR (50%) subsequently relapsed.

High-dose melphalan autografts At the time of the second autograft, 4 of the 46 (9%) patients were in CR and 31 (67%) in PR for an overall “chemosensitive disease” of 76% (35/46). After the second autograft, 12 (26%) patients entered CR and 30 (65%) PR for an overall response rate of 91 %. Overall, 35 (83%) patients relapsed from a previous CR or PR.

Overall response rates (CR + PR) at the time and after the non-myeloablative allograft and at the time and after the second autograft did not differ between the two cohorts (p=1 and p=0.54 respectively). However, the CR rate was significantly higher after the non-myeloablative allograft than after the second autograft (p=0.0026).
Salvage therapy

*Non-myeloablative allografts* Overall, 30 of the 58 patients were treated for disease relapse/progression after the non-myeloablative allograft. First-line salvage therapy consisted of bortezomib- or thalidomide-containing regimens in 19, standard chemotherapy and/or radiotherapy in 7, and 1 patient was treated with a rapid taper of the IS. Furthermore, 9 of these patients also received DLI. Three patients received DLI alone, and of them only 1 achieved a transient response.

After 1-3 lines of salvage therapy, 22 of 30 (73%) had a response, including 5 CR and 17 PR; 12 of 22 (54%) experienced a second relapse and 3 of 12 (25%) still showed responsive disease.

*High-dose melphalan autografts* Thirty-nine patients experienced relapse/progression after the second autograft. First-line salvage therapy consisted of bortezomib (n.8) - or thalidomide/lenalidomide-containing regimens (n.19) in 27 patients, and standard chemotherapy and/or radiotherapy in 10. One patient had not been treated and another patient was lost to follow up. Overall, 4 (11%) of the treated patients obtained a CR and 16 (43%) a PR for an overall response rate of 54%. Fourteen of these 20 (70%) patients experienced a second relapse.

Long-term clinical outcomes

At a median follow up of 7.1 (range 2.5 – 10.7+) years, median OS of the all 245 patients was 5.2 years, however, by intention-to-treat analysis, median OS and EFS were significantly longer in patients with HLA-identical siblings as compared with those without: not reached vs. 4.25 years (HR 0.51 , CI 95% 0.34–0.76, p=0.001) and 2.8 vs. 2.4 years (HR 0.62, CI 95% 0.44–0.87, p=0.005) (Figure 2A-B). By multivariate analysis, independent of age, gender, myeloma protein isotype, Durie&Salmon stage, and disease status at the first autograft; the presence of an
HLA-identical sibling and, therefore, the possibility of an allograft, was significantly associated with longer OS (HR 0.5, CI 95% 0.3-0.8, p=0.001) and EFS (HR 0.63, CI 95% 0.4-0.9, p=0.01) (Table 2). Disease status at the first autograft and myeloma protein isotype showed a significant impact on EFS.

At a median follow up of 7.3 (range 5.4 – 10.7+) years, median OS was not reached in the 58 patients who received a non-myeloablative allograft and 5.3 years (range 0.9-10.7+) in the 46 who received a second high-dose melphalan autograft (HR 0.55, CI 95% 0.32-0.94, p=0.02), whereas EFS was 39 months and 33 months (HR 0.62, CI 95% 0.40-0.96, p=0.02) respectively (Figure 2C-D). By multivariate analysis, patients who received the non-myeloablative allograft showed significantly improved OS (HR 0.56, CI 95% 0.3-1.0, p=0.04) and EFS (HR 0.60, 95% CI 0.4-0.9, p=0.02) when compared with those who received a second high-dose melphalan (Table 2).

The probability of a patient being alive in the original or in a subsequent CR or PR after salvage treatments following the non-myeloablative allograft and the second autograft is illustrated in Figure 3. At a median follow up of 3.9 years from relapse, OS was not reached and 1.7 years in patients who had relapsed after the non-myeloablative allograft and the second high-dose melphalan (HR 0.44, CI 95% 0.24-0.82, p=0.01) (Figure 3).

**Long-term immunosuppression**

Forty-one of 55 (74%) patients developed limited or extensive chronic GvHD. At 3 years from the allograft, 34 were alive, 15 were on IS and 19 were not. At the time of this report, 31 had reached a follow up of at least 5 years: 5 died while on IS whereas 23 were alive off IS and only 3 were still on IS (Figure 4). Overall, 19/29 (66%) discontinued IS because of resolution of chronic GvHD while 10/29 (34%) underwent a rapid IS taper after relapse.
DISCUSSION

Allografting in myeloma has hotly been debated since its clinical introduction.\textsuperscript{15} Lower relapses following allografts rather than autografts were already reported in the late 90’s, though this did not translate into better OS given the high TRM.\textsuperscript{16} Recently, reduced-intensity or truly non-myeloablative conditionings have been investigated.\textsuperscript{10,11,17,18}

Before the era of “new drugs”, whether non-myeloablative allografting could improve OS and EFS as compared to autografting was a matter of debate.\textsuperscript{19} In our study, treatment assignment was based only on the presence or absence of HLA-identical siblings. Neither induction treatments with “new drugs” nor currently used maintenance/consolidation therapies were included in the study. Previously reported results were encouraging.\textsuperscript{12} Here we have extended follow up to a median of 7 years.

Median OS of our entire study population was 5.2 years, consistent with the expected OS for patients diagnosed during the study period.\textsuperscript{20} At a median follow up of 7.1 years, both OS and EFS were significantly longer in patients with HLA-identical siblings than those without. Median OS was not reached in the allograft patients while EFS was 39 months. Both OS and EFS remained significantly longer as compared with those patients treated with two autografts who showed OS of 5.3 years and EFS of 33 months. Cavo et al. reported median EFS of 23 and 35 months after single and double autologous transplant respectively.\textsuperscript{21} However, it is important to point out that more recent reports on the use of maintenance therapy following autografting have shown remarkable improvements. McCarthy et al. reported an estimated median time to
progression of 42 months in patients treated with lenalidomide after a single autograft while Attal et al. reported a progression free survival of 42 months from the time of randomization in the arm with lenalidomide as maintenance as compared with 24 months in the placebo arm. These trials may define a new standard of treatment which includes maintenance after autografting. No definitive data are currently available on the use of new drugs after allografting.

Other studies comparing allografting with autografting have been reported. All included an autograft before a reduced-intensity allograft. The first published study by the IFM enrolled high-risk patients. A recent update showed no significant differences in EFS and OS with a trend for poorer survival in the allograft patients. One study by the PETHEMA group randomised 25 patients to receive the allograft and 85 a second autograft. All patients had failed to achieve at least near-CR after a first autograft. The median time for progression free survival and OS had not been reached in the allograft cohort, whereas they were 31 months and 58 months in the autograft group respectively.

Three other studies employed the “Seattle regimen” with low-dose TBI after a cytoreductive autograft. In the HOVON study, the control cohort was treated with one autograft followed by maintenance with thalidomide. An interim analysis showed no significant differences in EFS and OS between the two cohorts of 124 patients each: 39 % vs 34 % and 56 % vs 63 % at four years in the allograft group and the autograft-thalidomide group respectively. The recently closed EBMT study enrolled 107 patients with an HLA-identical sibling and 251 without from 26 European Centers. Eighty-eight and 104 patients completed the assigned treatments respectively. By intention-to-treat analysis and in those patients who completed the assigned treatment, the risk of relapse was significantly lower in the allograft cohort. Despite a
significantly higher TRM, 13% vs 5%, a trend for better OS was seen in the allograft cohort in both poor and good prognosis subgroups. Clinical findings of a large US multi-center trial from the Blood and Marrow Transplant Clinical Trials Network were recently reported.\textsuperscript{28,29} Seven-hundred-ten patients were randomised at 43 US transplant Centers. Induction treatments were not standardised and patients could be enrolled after HLA-typing between 3 and 9 months from the start of systemic induction therapy. Patients were defined as standard or high risk in the light of high beta-2-microglobulin levels and chromosomal abnormalities by standard cytogenetics. Both intention-to-treat and as-treated analyses showed equivalent 3-year progression free survival and OS in standard risk patients whereas there were trends in late progression free survival and time to progression in high risk patients who underwent allografting.\textsuperscript{28,29}

All these studies employed a “Mendelian” randomization, used as a surrogate for a more formal randomization.\textsuperscript{30} However, given substantial differences in the study inclusion criteria and treatment schemas, results are inevitably conflicting.

We reported the clinical outcomes of the entire young population of patients consecutively diagnosed at our Centers, regardless of the treatment protocol. This is rarely reported in phase II-III studies preventing the readers from knowing the proportion of patients actually eligible and eventually enrolled in a given protocol. We initially defined two patient cohorts with and without potential donors. This did not imply that all patients were eligible for investigational phase II-III studies either because of co-morbidities, patient will or donor eligibility. Of the patients enrolled in non-myeloablative allograft arm and in the tandem autograft arm, 96% and 78%, respectively, completed the assigned treatment. The inclusion of all eligible patients in the allograft cohort,
regardless of disease stage and prognostic factors, gave a good chance to capture the subset who most benefited from *graft-vs-myeloma* that resulted in long-term disease free survival. Unfortunately, our study was not designed to detect any myeloma-specific marker that could possibly predict plasma cell sensitivity to *graft-vs-myeloma*.

Chronic GvHD may be cause of long-term morbidity and poor quality of life. However, IS discontinuation because of its resolution greatly improves quality of life and may be used as a surrogate of the achievement of immunotolerance. Importantly, most of our surviving patients, at 5 years after the allograft, had discontinued IS because of continued resolution of GvHD.

Molecular remissions, prerequisite for cure, have more frequently been observed after myeloablative allografting rather than autografting with/without consolidation therapy.\textsuperscript{31-33} The cumulative risk of relapse at five years was 0% for patients with durable PCR-negativity after the allograft. We previously reported molecular remission after low-dose TBI allografting.\textsuperscript{34} Some remissions were reached months after transplant suggesting a gradual *graft-vs.myeloma* effect that may be less effective in bulky and aggressive diseases. A currently in progress large retrospective study on molecular responses will help define whether the intensity of the conditioning or *graft-vs.-myeloma* is more important to obtain molecular remissions.

After the introduction of “new drugs”, allografting has become a far less attractive option because of its toxicity. The role of allografting, however, may prospectively be evaluated in selected high risk patients where life expectancy remains very poor despite the use of bortezomib and lenalidomide.\textsuperscript{35} Though genetic abnormalities such as del(17p) were shown to have a
negative prognostic factor in a retrospective analysis on patients transplanted from both related and unrelated donors, the combination of allografting with “new drugs” has not yet been thoroughly explored. The efficacy of “new drugs” in patients relapsed after allografting has already been reported. Interestingly, we observed higher response rates to salvage therapies in the allograft patients and OS from relapse was significantly longer after the allograft than the second autograft (p=0.01). Though not part of a prospective trial, this finding may partly be explained by the hypotheses that the high percentage of donor T cells, usually seen at relapse after a non-myeloablative allograft, may synergize with immunomodulatory drugs and help restore \textit{graft-vs-myeloma} or that donor cells may favor the anti-myeloma effects of these drugs in the marrow milieu.

In summary, a subset of patients may have been cured with an allograft given the persistent disease free status extending up to longer than 10 years. However, given the risk of transplant-related toxicity and the recent remarkable advancements in newly diagnosed myeloma patients, the combination of allografting with new drugs should most preferably be explored in high risk patients, where life expectancy is poor, in prospective clinical trials.
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AUTHOR CONTRIBUTIONS

BB and MB contributed to the initial conception and designed the study. LG, FP, MR, RS, BA, FCS, MF, LB, SB, MA, AL, NM, AG, RF, MM, AP, RS, MB, and BB provided the study materials or patients. MR, RS, MF, LB, PO and BB collected and assembled the data. BB, BS, MR, RS, LG, MF, GC, RS and TG analysed and interpreted the data. LG, MF and BB wrote the manuscript. All authors gave the final approval to the manuscript.

DISCLOSURE

MB has received research support, consultant and scientific advisory board from Celgene and Janssen-Cilag. AP has received honoraria from Celgene, Janssen-Cilag, Merck, Amgen and advisory committee form Celgene and Janssen-Cilag. SB has received honoraria from Celgene, Janssen-Cilag, Novartis and Merck. The other authors have no potential conflicts of interest relevant to the article.
REFERENCES


Table 1.

<table>
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<td>Patients</td>
<td>245</td>
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<tr>
<td>Patients with siblings</td>
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<tr>
<td>HLA-typed patients</td>
<td>162 (81)</td>
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<td>Patients with/without donors</td>
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<tr>
<td>Male</td>
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<td>Mean age, years (range)</td>
<td>55 (30-65)</td>
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<td>Durie&amp;Salmon Stage III</td>
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<td>Non-secretory myeloma</td>
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<tr>
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<td>LDH above normal level</td>
<td>38/210 (18)</td>
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<td>Presence of Ch 13 deletion</td>
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Table 2: Univariate and multivariate analyses (Cox models)* for overall and event-free survivals in two cohorts: a) patients HLA-typed (n=162) and b) patients who completed their assigned treatments (n=104)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>Event-Free Survival</th>
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<tr>
<td></td>
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<td>a) 162 Patients HLA-typed</td>
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<td>Disease status at 1st autograft</td>
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<td>b) 104 Patients completed assigned</td>
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<td>▪ High-dose melphalan autograft</td>
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<tr>
<td>▪ Non myeloablative allograft</td>
<td>0.55 (0.3-0.9)</td>
<td>0.03</td>
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Abbreviations: HR: Hazard Ratio; CI: Confidence Interval.
* In both cohorts, multivariable HRs were adjusted for gender (male vs. female), age (<55 years vs. >55), Ig-G myeloma (Ig-G vs. others), Durie&Salmon stage (III vs. I or II), disease status pre 1st autograft (partial and complete remission vs. less than a partial remission).
**FIGURE LEGENDS**

**Figure 1.** CONSORT Diagram

**Figure 2.**
A. Overall survival and B. event free survival from the time of diagnosis of patients with an HLA-identical sibling (n. 80, solid line) and those without (n. 82, dotted line). C. Overall survival and D. event free survival of patients who received a non-myeloablative allograft (n. 58, solid line) and those who received a second high-dose melphalan autograft (n. 46, dotted line).

**Figure 3.** Probabilities of a patient being alive in the original complete or partial remission or in a subsequent remission due to salvage therapy after the non-myeloablative allograft (A) or the second autograft (B) calculated by the Couper method (dotted line). Black and grey solid lines represent overall and event free survivals by the Kaplan-Meier methods (see text). (C) Overall survival, calculated from first relapse, of patients who relapsed after the non-myeloablative allograft (solid line) and after the second high-dose melphalan autograft (dotted line).

**Figure 4.** Probability of being alive on or off immunosuppression (IS) medications among patients who developed limited or extensive chronic graft-vs-host disease (GvHD): overall incidence of chronic GvHD (dotted line); patients who died while on IS medications (black solid line); and patients alive who discontinued all IS medications (gray solid line) after developing chronic GvHD. The distance between the black and solid lines represents patients who are alive and still on IS medications (see also text).
Figure 1

- Newly diagnosed patients: 245
- Patients with siblings: 199
  - 37 not HLA-typed:
    - Refusal (n=9)
    - Early death/ineligibility for high-dose chemotherapy (n=14)
    - Ineligible donors (n=11)
    - Unknown (n=3)

- HLA-typed: 162
  - Patients with HLA-identical siblings: 80
  - Patients without HLA-identical siblings: 82

- Patients enrolled in auto-allo arm: 60
  - 58 completed

- Patients enrolled in double auto arm: 59
  - 46 completed
Figure 2
Figure 3

A

B

C

No. at Risk

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p=0.01
Figure 4
Long-term follow up of a comparison of non-myeloablative allografting with autografting for newly diagnosed myeloma

Luisa Giaccone, Barry Storer, Francesca Patriarca, Marcello Rotta, Roberto Sorasio, Bernardino Allione, Fabrizio Carnevale-Schianca, Moreno Festuccia, Lucia Brunello, Paola Omedè, Sara Bringhen, Massimo Aglietta, Alessandro Levis, Nicola Mordini, Andrea Gallamini, Renato Fanin, Massimo Massaia, Antonio Palumbo, Giovannino Ciccone, Rainer Storb, Ted A. Gooley, Mario Boccadoro and Benedetto Bruno