

# Update on Non-myeloablative Stem Cell Transplantation for Hematologic Malignancies

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## Abstract

Allogeneic stem cell transplantation is an established treatment modality for a variety of hematologic malignancies. Unfortunately it carries a high risk of complications and toxicities related to the intensive preparative regimen which is traditionally used for pre-transplant myeloablation and the graft versus host disease, which may be life threatening. Thus allogeneic stem cell transplantation has been used only for younger patients with a good performance status, excluding many other potential candidates due to advanced age or comorbid conditions. Non ablative or reduced intensity preparative regimens for allogeneic stem cell transplantation (NST) have been proposed as a strategy that would allow exploiting the graft versus tumor effect of allogeneic transplantation without the toxicity of myeloablative therapy. After more than five years of cumulative clinical experience, it is now well established that NST is a feasible treatment option for patients with suboptimal performance status and is mostly effective in slow proliferating malignancies, which gives time for a graft versus malignancy effect to take place. Additionally achievement of stable donor cell engraftment with NSTs provides a platform for adoptive immune cell treatments and may allow to extend indications of stem cell transplantation in the future.

*Key words:* Allogeneic transplantation; Non-ablative transplantation; Reduced intensity preparative regimen; Mini-transplant; Graft versus malignancy effect

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## 1. Introduction

High dose chemoradiotherapy (HDCR) followed by allogeneic hematopoietic stem cell (HSC) transplantation is an effective and potentially curative treatment for patients with hematological malignancies. It has also been successful in the treatment of non malignant hematological or metabolic diseases [1,2]. The curative effect of this treatment, traditionally was thought to be mediated by the tumoricidal effect of the chemotherapy. The stem cell transplantation was considered a means to overcome the myelotoxic effects of the chemo and radiation, providing reconstitution of hemopoiesis.

As early as 1960, using a murine leukemia model, it was shown that hematologic malignancies could be cured only with doses of total body irradiation that would be incompatible with life [3]. Barnes and Mathe using animal models and clinical observations respectively, hypothesized that beyond hematopoietic reconsti-

tution, allogeneic transplantation provides an anti-leukemic effect, mediated through the transplanted donor cells [4,5]. Until recently the existence of a graft versus malignancy effect in man was based on indirect evidence [6,7]. Direct evidence for a graft versus leukemia effect comes from the observation that donor lymphocytes infusion can reinduce remission in patients relapsing after allogeneic transplant, especially in patients with CML [8-13].

Allogeneic HSC transplant after myeloablative conditioning, is a curative option for many hematologic malignancies, however this modality is usually reserved for younger patients without serious comorbid conditions. The increased morbidity and mortality associated with older age, are the main reasons for not transplanting older patients or medically debilitated patients [14]. In animal models the incidence of GVHD mortality and morbidity is related to the intensity of the preparative regimen, and non ablative regimens in animal models

have been developed that allow stable engraftment of donor stem cells [15-18]. Thus a strategy utilizing a less intensive, non-myelosuppressive preparative regimen that was sufficiently immunosuppressive to prevent graft rejection and allow engraftment of HSC would be a rational clinical model to explore the efficacy of the graft versus malignancy effect in patients with hematologic malignancies ineligible for high dose chemotherapy or radiation because of age or concurrent medical conditions. In this review we summarize the published experience in the field of NST, its current applications and future areas for development.

## 2. Development of Conditioning Regimens and Post Transplant Immunotherapy in Nonmyeloablative Stem Cell Transplantation (NST)

Non-myeloablative stem cell transplantation, has shown that engraftment can occur with immunosuppression and minimal myelosuppression. However the optimum doses and the best agents required to achieve engraftment in different clinical situations has not yet been defined and is probably not the same for all patients. Depending on the aggressiveness of the underlying malignancy and the genetic disparity between donor and recipient there is a continuum of non-ablative, reduced intensity and full ablative regimens that have been used in the context of stem cell transplantation. Most NST regimens reported to date have included been either purine analogue based or low dose TBI based [23-35].

### 2.1. NST in Acute Leukemia/MDS

From April 1996 to January 2000 31 patients received one of two preparative regimens depending on prior exposure to fludarabine [35]. Twenty patients who either had no prior exposure to fludarabine or had responded to fludarabine based chemotherapy, received fludarabine, cytarabine and idarubicin. Eleven patients with prior fludarabine exposure received cladribine 12 mg/m<sup>2</sup> for 5 days by continuous infusion with cytarabine 1 g/m<sup>2</sup> daily. All patients received bone marrow or mobilized peripheral stem cells from an HLA identical or 1 antigen mismatch related donor after completion of chemotherapy. GVHD prophylaxis consisted of cyclosporine or tacrolimus with either steroids or methotrexate. Neutrophil recovery occurred in 29 patients at a median of 13 days post-transplant (range 8-38 days) and 25 patients achieved platelet transfusion independence after a median of 17 days (range 8-78 days). Chimerism analysis on day 30 revealed that 20 patients had between 80% and 100% donor cells, 1 patient had 40% donor cells and 2 patients had no evidence of donor cell engraftment. Two patients with >90% engraftment had late autologous reconstitution by 3 months without evidence of relapse, all other patients in remission remained with >90% donor cell engraftment.

Toxicity was minimal with only one treatment related death. Acute GVHD grade  $\geq 2$  occurred in 6 patients,

one patient died as a result of this complication. Four of these 6 patients were recipients of bone marrow from mismatched related donors.

Complete remission (as defined by <5% bone marrow blasts, neutrophil recovery and platelet transfusion independence) was obtained or continued in 24 patients. Thirteen of these patients relapsed at a median of 3.6 months (range 1.4-17.2 months). At one year the overall survival for the whole group is 47% and the disease free survival is 34%. The most important prognostic factor for survival was disease status at the time of transplant. Patients who were in remission or untreated first relapse when they received their transplant had a better outcome than those with refractory disease. Death resulted from disease (n=15), infection (n=3), toxicity (n=1), GVHD (n=1) and graft failure (n=1).

In an effort to improve outcomes for patients with refractory disease a more intensive combination of fludarabine with melphalan was explored [36]. The rationale of this regimen was to provide more sufficient myelosuppression for a better short-term leukemia control, which would allow successful engraftment and anti-leukemic effect of allogeneic stem cells, including those from unrelated donors. Forty-three AML/MDS patients were treated between 4/96 and 2/00. All were ineligible for conventional transplant due to age or co-morbid conditions. Only one patient was in 1<sup>st</sup> complete remission, 10 patients were in untreated 1<sup>st</sup> relapse, 5 patients were in 2<sup>nd</sup> or subsequent remission, and 27 were in refractory relapse.

Preparative regimen consisted of fludarabine with melphalan (180 or 140 mg/m<sup>2</sup>) for 37 patients or cladribine (12 mg/m<sup>2</sup> daily for 5 days) with melphalan for 6 patients. The latter preparative regimen was soon abandoned because of excessive toxicity. Patients received progenitor stem cells from HLA identical or 1 antigen mismatch related donors, or from HLA identical unrelated donors. GVHD prophylaxis consisted of tacrolimus and methotrexate for the majority of the patients. Two-year survival and disease free survival (DFS) was 36% and 34% respectively. Patients with sensitive disease had 55% long term survival and patients with refractory disease had 20% DFS at 2 years post transplant.

Data from the European Bone Marrow Transplant Registry (EBMTR) were recently presented by Rezvani et al. One hundred and forty-nine patients [37] with acute leukemia or MDS underwent non-myeloablative stem cell transplants from April 1994 to May 2000. Sixty-nine patients had AML, 40 ALL and 45 MDS.

Eighty-six percent of the patients received fludarabine based preparative regimens followed by allogeneic stem cells from an HLA identical sibling in 80%, an HLA matched unrelated donor in 12% and other donors in 8% of the cases. GVHD prophylaxis was consisted of cyclosporine and methotrexate in 91% of the cases.

Seven percent of the patients experienced primary graft failure and durable donor cell engraftment (>95% donor cells) was seen in over 77% of the patients. GVHD grade III or IV occurred in 18% of the patients with an overall survival of 35% at 18 months.

These results underscore the fact that patients with refractory leukemias have a higher relapse rate and poor long-term outcomes with NST, but patients with chemosensitive disease can have long term disease control [36].

## 2.2. NST in CML

CML would seem to be the ideal disease for exploration of NST, since it has a chronic course and is extremely sensitive to DLI, at least in the chronic phase. At MDACC 10 patients with CML have been treated with NST using the FLAG-ida regimen that was used for the AML/MDS patients. All patients were ineligible for conventional transplantation due to age or comorbid conditions [38]. The median age of the patients was 59 years (range 42-72), and all had failed prior interferon therapy. All patients achieved neutrophil engraftment at a median of 13 days (range 10-31) and all became platelet transfusion independent at a median of 14 days (range 9-68). 4 of the 5 patients transplanted in chronic phase achieved complete cytogenetic remission; three of them still survive, 2 in complete remission, 1 alive with disease. Of the 5 patients transplanted in transformed phase none are alive in remission.

The combination of fludarabine/melphalan has also been studied at MDACC in 27 patients with CML [36]. The 2-year survival and disease free survival for these patients was 40% and 38% respectively. Patients transplanted in 1<sup>st</sup> chronic phase had more than 60% disease free survival while patients with transformed disease had a 30% of long term disease free survival.

Slavin et al from Hadassah recently published their experience with non-myeloablative allogeneic stem cell transplantation for patients with CML [40]. Twenty-one patients, potentially eligible for conventional myeloablative transplantation, with a median age of 39 (range 3-57), in 1<sup>st</sup> or stable 2<sup>nd</sup> chronic phase, were entered to the study. They were treated with a preparative regimen consisting of fludarabine 30 mg/m<sup>2</sup>x6 days, oral busulfan 4 mg/kg/dayx2 days and rabbit anti-human T-cell globulin 5-10 mg/kg/dayx4 days. GVHD prophylaxis consisted of cyclosporine A (CSA) starting on day 1 with a rapid tapering schedule [41]. All patients had rapid and stable engraftment, with minimal toxicity. Acute GVHD was observed in 12 patients (5 grade IV) and chronic GVHD in 9 patients (severe in 3). Two patients died of GVHD on days+96 and +116. All patients achieved cytogenetic and molecular remissions. Only 1 patient had molecular relapse which was reversed with DLI. Actuarial probability of survival and disease-free survival at 4 years was 87%.

Based on a canine model, researchers at the Fred Hutchinson Research Center have used a low dose TBI preparative regimen, as a novel strategy for conditioning in high-risk patients with indications for allogeneic stem cell transplant [29]. Of the first 50 patients treated with 200 Gy of TBI alone followed by infusion of PBSC from an HLA identical donor, they observed a 20% incidence of graft failure. After addition of fludarabine

to the low dose TBI the incidence of graft failure decreased to 0% for HLA-identical siblings and 12% for the recipients of a matched unrelated donor's graft [30]. Recently Sandmaier et al presented their experience with CML patients treated with a low dose TBI containing regimen [42]. Twelve patients, median age 56 years (range 40 to 71), ineligible for conventional transplantation due to age or comorbid conditions, were enrolled in this treatment protocol. Eight patients were in chronic phase and four in accelerated phase. Preparative regimen for the first seven of them was 200 Gy TBI alone at day 0. Due to non-fatal graft rejections in 4 of these 7 patients, fludarabine at a dose of 30 mg/m<sup>2</sup>/dayx3 days (-4, -3, -2) was added to the preparative regimen of the 5 other patients. All patients received peripheral stem cells from an HLA identical sibling. GVHD prophylaxis consisted of mycophenolate mofetil (days 0 to 27) and cyclosporine (days -1 to 56).

All patients achieved initial donor cell engraftment. Four of the patients as stated above had a non-fatal graft rejection. Donor T-cell chimerism was higher for the 5 patients that received fludarabine/TBI as compared to those that received only TBI. The regimen was very well tolerated. Six of the 8 patients with sustained grafts, developed acute GVHD grade II-IV which responded to therapy in all but 1 case.

All patients with sustained grafts achieved cytogenetic and molecular remissions. After a median follow up of 421 days (111-621), 8 patients are alive and 6 of them are disease free, 2 had graft rejection. Death resulted from disease progression in 2 patients, infection in 1 patient and GVHD in 1 patient.

The group at the National Institutes of Health at Bethesda reported on thirteen CML patients who were treated with a non-myeloablative preparative regimen of fludarabine and cyclophosphamide. Patients' median age was 34 (range 15-67) [43]. Eight patients were in initial chronic phase and five with advanced disease. Preparative regimen consisted of fludarabine 25 mg/m<sup>2</sup>/day for 5 days and cyclophosphamide 60 mg/kg/dayx2 days. All patients received peripheral stem cells from an HLA identical sibling donor. All patients engrafted, but 2 had graft rejection and autologous hematopoietic reconstitution. Toxicity was minimal with no treatment related mortality. Six patients had grade II-IV acute GVHD which resolved with treatment and five patients developed limited chronic GVHD. Three out of 5 evaluable patients transplanted in CP1 achieved complete molecular remission and only 1 of the more advanced CML achieved cytogenetic remission, after an average follow-up of 285 days.

Forty-five CML patients were reported to the German Cooperative Group Registry; most of these patients were ineligible for conventional transplantation. 20 patients were in 1<sup>st</sup> chronic phase and 25 had more advanced disease [44]. 80% of the patients received conditioning regimen consisted of fludarabine and busulfan. Eighteen patients received HLA matched related donor cells, 2 received mismatch related and 25 received matched unrelated donor cells. GVHD prophylaxis was cyclosporine

based and 20 patients received also anti-thymocyte globulin. Twenty-two patients developed grade II to IV GVHD, and there was a high incidence of graft failure (10/45) and severe infections (13/45). After a median follow-up of 9 months sixteen patients died due to progressive disease (n=3) or from treatment related reasons (n=13). Disease free and overall survival was 34% and 62% respectively at 1 year, in this high-risk patient population.

Forty-six patients with CML undergoing NST were reported to the EBMT [45]. Median age of the patients was 50 (range 29-62). 23 of the patients were in 1<sup>st</sup> chronic phase. Preparative regimen consisted of fludarabine, melphalan for 31 patients (67%) and fludarabine busulfan for 8 patients. Thirty-three patients received an HLA identical graft, 10 patients received matched unrelated grafts and 1 patient mismatched unrelated graft. Most of the patients received cyclosporine based GVHD prophylaxis and all recipient of unrelated donor cells received T-cell depleted grafts. All patients engrafted, with 32 out of 39 patients having >95% donor cell chimerism. Acute GVHD grade II-IV occurred in 24% of the patients. Transplant related mortality at one year was 35%. Overall survival and relapse rates were favorable for younger patients and patients in 1<sup>st</sup> chronic phase of their disease.

The current experience with NST in CML patients shows that it is a feasible treatment option for older patients. Graft versus host disease still occurs, but non-relapse mortality seems to be lower than that seen after conventional preparative regimens. Non ablative regimens for CML should continue to be explored in clinical trials, but should not replace conventional myeloablative regimens which historically is considered the only proven curative treatment for CML.

### 2.3. NST in Lymphoid Malignancies

Among lymphoid malignancies, low-grade lymphoma appears most susceptible to graft-versus-malignancy effects [46]. Most recently the MDACC experience was reviewed using a non-myeloablative preparative regimen of fludarabine (25 mg/m<sup>2</sup>/d for 5 consecutive days) in combination with cyclophosphamide (1,000 mg/m<sup>2</sup>/d for the last two days of fludarabine treatment) in patients with low-grade lymphomas [47]. Eleven patients, median age 51 years (range 36-67) were enrolled in this protocol. Ten had follicular and one had small lymphocytic lymphoma. All patients had relapsed after prior response to conventional treatment. All patients had received salvage chemotherapy and had stable or responding disease. Unmanipulated, peripheral blood stem cells, from an HLA identical sibling donor, were administered 48 hours after the chemotherapy. GVHD prophylaxis consisted of tacrolimus and mini MTX. Early tapering of tacrolimus was planned by day 60-90 if there were signs of residual disease. No treatment related mortality was observed. Neutrophil engraftment was achieved after a median of 11 days [10-16] post transplant and platelet transfusion requirements were li-

mitted to only three patients who promptly recovered platelets after 1 to 4 transfusions. The median percentage of donor cells at one-month post transplant was 80%. Acute GVHD $\geq$ 2 occurred only in one patient with skin GVHD. All patients achieved CR, and are alive and in remission with a median follow up of 16 months. The minimal toxicity and the high response rate of this truly nonmyeloblastic regimen is a promising therapy for low grade lymphomas, even for elderly patients, deserving further studies with long term follow up.

Fifteen patients with aggressive lymphomas have been treated using non ablative regimens at MDACC [48]. All patients were older than 50 years of age or had comorbid conditions which precluded them from high dose chemotherapy. Median age was 55 years (range 31-64). Seven patients had diffuse large cell lymphoma, 1 had anaplastic large cell lymphoma, 4 had diffuse mantle cell and 3 had CLL in Richter's transformation. The preparative regimen consisted of cisplatin 100 mg/m<sup>2</sup>/day CI for 4 days, fludarabine 30 mg/m<sup>2</sup>/day for 2 days and cytarabine 500-1,000 mg/m<sup>2</sup>/day for 2 days (PFA). All patients received peripheral blood stem cells from an HLA identical sibling donor. Tacrolimus and methotrexate were used for GVHD prophylaxis. One case of primary and one case of secondary autologous reconstitution was observed. Acute GVHD grade II occurred in 2 patients after transplant and both responded to treatment. Six of the 15 patients are alive and disease free. These data show that PFA at conventional dosage, can induce high rate of engraftment of allogeneic stem cell transplantation with acceptable GVHD. The regimen seems to be effective and needs further evaluation.

The cumulative results for NSTs in lymphoid malignancies, from the European registry were recently reviewed [49]. 115 patients with a variety of lymphoid malignancies were reported to the EBMT. Median age was 38 years (range 3-61). 28 patients had low-grade lymphoma, 39 had high grade lymphoma, 9 had mantle cell lymphoma and 39 had Hodgkin's disease. The patients had a median of 3 prior treatment courses and 66.7% had chemosensitive disease. 92% of the patients received preparative regimen which included fludarabine and an alkylating agent. GVHD prophylaxis consisted of cyclosporine with or without methotrexate/anti-lymphocyte globulin. A 20% risk of grade II-IV acute GVHD and a non relapse mortality rate of 28% at 1 year was observed. Causes of transplant related mortality were GVHD (55%), infection (30%) and multiorgan failure (15%). After a median follow up of 106 days 31 patients had relapsed and 18 of them died. The high relapse rate and the relatively high transplant related mortality rate, underscore the need for prospective randomized trials before this strategy can be considered standard care for patients with lymphoid malignancies.

Twenty patients with CLL were reported in a multicenter study from Germany [49]. Median age of the patients was 50 years (range 34-62), median number of prior chemotherapies was three. Conditioning regimen

included fludarabine, busulfan and anti-thymocyte globulin. Nine patients received cells from an HLA identical sibling, 1 from a non HLA-identical related donor, and 10 from matched unrelated donors. GVHD prophylaxis consisted of cyclosporine alone or in combination with methotrexate or MMF. Engraftment was prompt with only one instance of graft failure from a patient who received matched unrelated donor cells. Toxicity was acceptable, but there was a 50% incidence of grade II-IV and 25% incidence of grade III-IV GVHD. After a median follow up of 7 months 2 patients died; one from GVHD and one from progressive disease. Sixteen of the 20 patients achieved remission.

These data on NST for lymphoid malignancies, support that it is a feasible treatment option for relapsing patients with responsive disease to conventional chemotherapy. The high incidence of GVHD that was observed in these patients underscores the importance of limiting these therapies to centers with extensive experience with conventional allografting. Delayed responses from a graft versus leukemia effect, sometimes several months after the initial transplant, might occur. Further studies and comparative trials are warranted. Overall patients with low grade lymphomas and chemo-responsive disease appear to be mostly benefited from NSTs.

#### 2.4. NST in Multiple Myeloma

The existence of a graft versus myeloma effect has been well documented [51,52], but has been difficult to exploit because of the high incidence of non relapse mortality with conventional myeloablative stem cell transplant in this disease.

Twenty-three myeloma patients median age 50 years (range 45-64), ineligible for conventional transplantation due to age or comorbid conditions were included in this treatment protocol. All but 1 patient were heavily pre-treated and had relapsed by the time of transplantation. Ten of them had received prior autologous stem cell transplant. Preparative regimen was consisted of fludarabine 25 mg/m<sup>2</sup> for 5 days and melphalan 140 mg/m<sup>2</sup> or 180 mg/m<sup>2</sup>. Thirteen received graft from an HLA identical related donor, one from a 1 antigen mismatch related donor, and 9 from an HLA identical unrelated donor. GVHD prophylaxis consisted of tacrolimus and methylprednisolone or tacrolimus and methotrexate. ATG was given to the recipients of unrelated donor grafts. Engraftment was prompt and all evaluable patients [20] achieved complete donor chimerism. Toxicity was acceptable but acute GVHD grade II-IV occurred in 13 patients and grade III or IV in 4 patients. Five patients developed chronic GVHD. Nine patients died of treatment related causes. Sixteen patients responded to the treatment, and 7 of them had a complete response. After a median follow up of 6.5 months (range 1-41), six patients are still alive and in remission.

Molina et al reported results from Seattle and City of Hope [52]. Twelve patients with previously treated myeloma, median age 49 (range 40-63) were included

to the study. All patients were initially treated with high dose melphalan (200 mg/m<sup>2</sup>) followed by autologous stem cell rescue. Forty to 120 days later the patients were given a single non-myeloablative dose of 2 Gy total body irradiation. All patients received peripheral stem cells from HLA identical siblings. GVHD prophylaxis consisted of MMF (28 days) and cyclosporine (56 days). All patients engrafted promptly after the allografts with sustained donor cell chimerism. Toxicities were acceptable but acute GVHD grade II occurred in 6 patients and grade IV in 2 patients. With a median follow up of 7 months, 3 patients died, from progressive disease or from grade IV GVHD. Overall 6 patients achieved complete response and another 4 partial disease response. This study provides the proof of principle that this approach is feasible and complete responses and donor cell engraftment can be achieved with a low level of non-relapse mortality.

Lalancette et al [53] reported their experience with 50 myeloma patients that underwent NST in 20 centers. Median age of the patients was 48 [33-62]. 29 of the patients were transplanted in 1<sup>st</sup> [14] or subsequent [15] remission. Forty-two patients received fludarabine containing conditioning regimens, with either melphalan (24 patients) or busulfan [17]. Forty-three patients received stem cells from an HLA identical sibling and 6 from a matched unrelated donor. Most of the patients received cyclosporine for GVHD prophylaxis, 26 were given ATG/ALG, and 17 received Campath 1H. All evaluable patients engrafted. Twenty of 27 patients achieved more than 95% donor cell chimerism. Grade II-IV GVHD occurred in 28% of the patients. For the patients with chemosensitive disease the transplant related mortality was 13% only as opposed to 67% for the poor risk patients. Overall survival at 1 and 2 years was 54% and 40% respectively. Thirty-six patients achieved [23] or sustained [13] remissions and 4 patients were refractory to treatment. Relapse rate was 13% at 1 year and 11 patients underwent DLI with 2 of them achieving complete remissions.

The European registry data confirm the feasibility of NST in myeloma patient and the efficacy in patients with chemosensitive disease [53].

Twenty-three patients were treated in a multi-center study from the United Kingdom [54]. Median age was 47 years (range 34-58), 10 patients had relapsed after previous transplants and another 7 had primary refractory disease. All patients received preparative regimen consisted of fludarabine and melphalan as well as CAMPATH-1H for GVHD prophylaxis. Seventeen patients received grafts from an HLA matched sibling and 6 patients from a matched unrelated donor. All patients engrafted successfully. Only 2 patients developed grade II (maximum) acute GVHD. After a median follow up of 7 months 6 patients died from transplant related causes. Five out of 19 evaluable patients achieved a CR. Progression free survival at 1 year was 42%. This study demonstrates that the use of CAMPATH-1H can reduce the incidence of severe GVHD after NST.

Schaefer et al [55] reported their experience with

NST in myeloma patients. They treated 22 heavily pre-treated patients whose median age was 54 (range 32-66). They used single low dose TBI (2 Gy, day-1) with cyclophosphamide (day-3, -2) and fludarabine (day -9 to -5) as preparative regimen. Sixteen of the patients received a matched unrelated donor graft and 6 a graft from an HLA matched relative. GVHD prophylaxis consisted of ATG and cyclosporine. All but one patient engrafted and full donor chimerism was observed in 16 out of 19 patients. There was a 27% transplant related mortality rate for the first 100 days post-transplant. After a median follow up of 5.5 months, 12 patients (9 of them from unrelated donor transplants) died due to progressive disease (n=5) or from transplant related causes (n=7). Severe GVHD grade III or IV occurred only in 1 patient. Eight patients achieved at least partial response to the transplant.

Badros et al from Little Rock [56] reported their experience with NST in myeloma patients, using melphalan 100 mg/m<sup>2</sup> alone. They treated 16 high-risk myeloma patients who had relapsed after a single [7] or tandem [9] autotransplants; the median age was 57 years (range 42-70). All patients received melphalan 100 mg/m<sup>2</sup> as preparative regimen and received peripheral stem cells from HLA identical siblings. Additional donor stem cells were given by days 21, 42 and 120 in patients without GVHD. Cyclosporine from day -1 to day 60 was used as GVHD prophylaxis. All but 1 patient engrafted promptly. Fifteen of them achieved full donor chimerism and one patient had autologous hemopoietic reconstitution after receiving back up autologous cells. Eight patients (50%) developed grade II to IV GVHD and six patients developed chronic GVHD. After a median follow up of 11 months, 2 patients died of progressive disease and 3 died from GVHD (n=3). Nine patients responded with partial, or complete remission. The existing experience shows that non-ablative or reduced intensity conditioning regimens are feasible in myeloma, however further studies will be needed to define the role of this therapeutic modality in the treatment of multiple myeloma.

### 3. Conclusions

Non ablative stem cell transplantation is a novel therapy. Currently around 1500 patients have been reported. It has been proven to have acceptable toxicity and to be well tolerated by patients with suboptimal performance status or advanced age. The first experience gives us the insight as to when or where this is an effective option, however the indications of NST have not yet been clearly defined. Patients with aggressive malignancies, refractory at the time of transplantation seem not to benefit from this procedure. Hematologic malignancies which have established benefits with high-dose ablative transplant regimens, should be treated with NST only in elderly or debilitated patients. Lymphoid malignancies on the other hand, like CLL, low grade and mantle cell lymphomas seem to respond to NST, and the encouraging data presented above supports

further testing in patients of all ages.

NST might also be used as a platform for adoptive immune cell treatments once establishing stable donor cell chimerism. The comparative low toxicity profile of NSTs allows for exploration of a graft versus malignancy effect in non hematologic tumors, with promising results in the case of renal cell carcinoma. GVHD, graft rejection and disease recurrence continue to be the most important causes of treatment failure.

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