cells. Cancer Res 2000;60:549-52.
10. Falzetti D, Crescenzi B, Matteuci C, Falini B, Martelli MF, Van Den Berghe H, et al. Genomic instability and recurrent breakpoints are main cytogenetic findings in Hodgkin's disease. Haematologica 1999;84:298-305.
11. Drexler HG. Recent results on the biology of Hodgkin and Reed-Sternberg cells. I. Biopsy material. Leuk Lymphoma 1992;8:283-313.
12. Martin-Subero JI, Klapper W, Sotnikova A, Callet-Bauchu E, Harder L, Bastard C, et al. Chromosomal breakpoints affecting immunoglobulin loci are recurrent in Hodgkin and Reed-Sternberg cells of classical Hodgkin lymphoma. Cancer Res 2006;66:10332-8.
13. Renne C, Martin-Subero JI, Eickernjäger M, Hansmann ML, Küppers R, Siebert R, et al. Aberrant expression of ID2, a suppressor of B-cell-specific gene expression, in Hodgkin's lymphoma. Am J Pathol 2006;169:655-64.
14. Schmitz R, Renne C, Rosenquist R, Tinguely M, Distler V, Menestrina F, et al. Insights into the multistep transformation process of lymphomas: IgH-associated translocations and tumor suppressor gene mutations in clonally related composite Hodgkin's and non-Hodgkin's lymphomas. Leukemia 2005;19:1452-8.
15. Jansen MP, Hopman AH, Bot FJ, Haesevoets A, Stevens-Kroef MJ, Arends JW, et al. Morphologically normal, CD30-negative B-lymphocytes with chromosome aberrations in classical Hodgkin's disease: the progenitor cell of the malignant clone? J Pathol 1999;189:527-32.
16. Emmerich F, Meiser M, Hummel M, Demel G, Foss HD, Jundt F, et al. Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. Blood 1999; 94:3129-34.
17. Martin-Subero JI, Wlodarska I, Bastard C, Picquenot JM, Hoppner J, Giefing M, et al. Chromosomal rearrangements involving the BCL3 locus are recurrent in classical Hodgkin and peripheral T-cell lymphoma. Blood 2006;108:401-2.
18. Weniger MA, Melzner I, Menz CK, Wegener S, Bucur AJ, Dorsch K, et al. Mutations of the tumor suppressor gene SOCS-1 in classical Hodgkin lymphoma are frequent and associated with nuclear phospho-STAT5 accumulation. Oncogene 2006;25:2679-84.
19. Lemoine FJ, Marriott SJ. Genomic instability driven by the human T-cell leukemia virus type I (HTLV-I) oncoprotein, Tax. Oncogene 2002;21:7230-4.
20. Bose S, Starczynski J, Chukwuma M, Baumforth K, Wei W, Morgan S, et al. Down-regulation of ATM protein in HRS cells of nodular sclerosis Hodgkin's lymphoma in children occurs in the absence of ATM gene inactivation. J Pathol 2007;213:329-36.
21. Dutton A, Woodman CB, Chukwuma MB, Last JI, Wei W, Vockerodt M, et al. Bmi-1 is induced by the Epstein-Barr virus oncogene LMP1 and regulates the expression of viral target genes in Hodgkin lymphoma cells. Blood 2007;109: 2597-603.
22. Lavin MF, Birrell G, Chen P, Kozlov S, Scott S, Gueven N. ATM signaling and genomic stability in response to DNA damage. Mutat Res 2005;569:123-32.
23. Janz M, Stühmer T, Vassilev LT, Bargou RC. Pharmacologic activation of p53-dependent and p53-independent apoptotic pathways in Hodgkin/Reed-Sternberg cells. Leukemia 2007;21:772-9.
24. Montesinos-Rongen M, Roers A, Küppers R, Rajewsky K, Hansmann ML. Mutation of the p53 gene is not a typical feature of Hodgkin and Reed-Sternberg cells in Hodgkin's disease. Blood 1999;94:1755-60.

Allogeneic transplantation in multiple myeloma

Gösta Gahrton and Bo Björkstrand

Department of Medicine, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden

doi: 10.3324/haematol.13555

Allogeneic hematopoietic stem cell transplantation has been performed for the treatment of multiple myeloma since the early 1980s. We performed our first myeloma transplant in April 1983.[1] The patient, a 46-year old woman, was diagnosed with monoclonal gammopathy of undetermined significance in 1974. The disease progressed to multiple myeloma and the patient required treatment with melphalan and prednisone in 1977. In 1982 the disease was resistant to chemotherapy and in early 1983 she received a bone marrow transplant from an HLA-identical brother. She engrafted without serious complications, and at the time of publication of her case report in 1986 she was in complete hematologic remission with no signs of disease. We thought that we had cured the first patient with multiple myeloma, but 4 years after the transplant she relapsed. She lived for another 6 years as a mixed chimera, but eventually died from the disease. Since then numerous allogeneic transplants have been performed throughout the world. The registry of the European Group of Blood and Marrow Transplantation (EBMT) has reports of more than 4000 transplants performed in European centers.

Allogeneic transplantation using myeloablative conditioning

The idea of using high-dose myeloablative allogeneic transplantation in multiple myeloma has four rationales. First, the myeloablative chemotherapy and total body irradiation should eradicate the myeloma cells in the bone marrow. Second, reduction of host immunocompetent cells should allow engraftment of the allogeneic cells. Third, the graft should save the patient from the effect of ablation of normal host bone marrow cells. Fourth, the immunocompetent donor cells should help eradicate myeloma cells (through a graft-versus-myeloma [GVM], effect) that might persist despite the myeloablative therapy. Originally the most common myeloablative conditioning therapy was cyclophosphamide + total body irradiation (10-12 Gy), fractionated or unfractionated with lung shielding. However, many other myeloablative protocols have subsequently been developed.

Initially it appeared that all these four goals could be obtained in multiple myeloma. However, as in the case described above, it soon became apparent that this rarely happens. One problem is the high incidence of severe graft-versus-host disease (GVHD) and high transplant-related mortality, which reached 30-40%. Another problem was the significant relapse/progression rate.[2] Although the relapse/progression rate was shown to be lower with allogeneic transplantation than with autologous transplantation already in 1996 in an EBMT retrospective case-matched analysis of 378 patients, the overall survival was, at that time, inferior

due to the high transplant-related mortality.[3] However, in females the treatment-related mortality was lower than in males, and in fact there was no significant difference in overall survival between female autologous and allogeneic transplants recipients. Long-term survival also appeared better in allogeneic transplants than in autologous transplants in females, and was 30% at 9 years in those undergoing allotransplantation. Later a large retrospective EBMT study[4] confirmed the comparatively good results in females, in particular in female-to-female transplants, while the worst results occurred in male patients irrespective of donor, apparently due to a lower relapse rate but higher transplant-related mortality in sex-mismatched recipient – donor combinations, and the reverse in sex-matched male transplants. These differences seem to be due to the presence of female donor T cells that are specific for male minor histocompatibility antigens (H-Y) encoded by male Y chromosome genes. Attempts are presently being made to use or modulate minor histocompatibility antigens to improve the GVM effect.[5]

The main causes of death following myeloablative allogeneic transplantation are severe infections, often combined with severe GVHD. New supportive treatment modalities in later years, for example new antibiotics, and better GVHD prevention methods, seem to be the reason why myeloablative allogeneic transplant results improved dramatically over time, as shown in a comparison by the EBMT of transplants performed before and after 1994.[6] Transplant-related mortality was reduced significantly, and the median overall survival for the later transplants was 50 months. However the transplant-related mortality was still high and myeloablative allogeneic transplantation is, therefore, now only rarely performed.

Molecular remission

Studies by Corradini *et al.*[7] showed that molecular remissions are more frequent after myeloablative allogeneic transplantation than after autologous transplantation although the intensity of the conditioning regimens is similar. Using clonal markers based on the rearrangement of immunoglobulin heavy-chain genes generated for each myeloma patient at diagnosis and used for polymerase chain reaction (PCR) detection of residual myeloma cells after transplantation, it was shown that out of 29 patients who entered hematologic remission after transplantation nine out of 14 who underwent allogeneic transplantation entered molecular remission and two out of 15 who had an autologous transplant did so. In three of the allogeneic transplants, molecular remission occurred more than 3 years after the transplant, while late molecular remissions were not seen in autologous transplant recipients, indicating a GVM effect in the allogeneic transplants. Another study[8] found that in 48 patients who obtained a hematologic remission following allogeneic transplantation, 16 (33%) obtained durable PCR-negativity after transplantation, while 13 (27%) remained persistently PCR-positive, and 19 (30%) showed a mixed pattern. The cumulative risk of relapse at 5 years was 0% for PCR-negative patients, 33% for PCR-mixed patients and 100% for PCR-positive patients. These studies show that molecular remission is more common after allogeneic transplantation and that molecular remission predicts a longer relapse-free survival. Thus, attempts to induce molecular remission seem important, although the studies do not give an answer to the question of whether it is the myeloablation or the GVM that is the more important factor for obtaining such a remission.

Thus, the lessons from these studies are three-fold. First, attempts to reduce the transplant-related mortality are crucial. Secondly, there is a GVM effect, and thirdly, molecular remissions are important and, therefore, any approach to cure multiple myeloma should aim to induce not only hematologic remission but also molecular remission.

Reduced intensity condition allogeneic transplantation – non-randomized studies

Based on the idea that the GVM effect may be more important than the intensity of the conditioning regimens, the Seattle Group developed an allogeneic transplant modality using considerably lower intensity in the conditioning regimen than had previously been used, i.e. 2 Gy total body irradiation, followed post-transplant by GVHD prevention with mycophenolate mofetil and cyclosporine.[9] Transplant-related mortality was reduced significantly. Recently they used this regimen with fludarabine (30 mg/m^2 x 3) added in the conditioning in 24 refractory or relapsed patients who received an allogeneic transplant from an unrelated donor either preceded by an autologous transplant (13 patients) or directly (11 patients).[10] At 3 years of follow-up, the overall survival rate was 61% for all patients and was better in the group of patients who had undergone tandem transplantation (77%).

Kröger *et al.*[11] used a somewhat different conditioning i.e.melphalan 100-140 mg/m^2 + fludarabine 30 mg/m^2 x 5 in 57 patients. Some patients received antithymocyte globulin (ATG) and other patients alemtuzumab. The treatment-related mortality was 11% at 100 days and 70% at 1 year in their first report, i.e. considerably lower than that seen after myeloablative conditioning. Fifty-five percent of the patients obtained a complete remission and 27% a partial remission, giving a response rate of 82%. The updated overall and disease-free survival was 68% and 42%, respectively, at 1,500 days with only a slightly poorer overall survival for recipients of grafts from unrelated donors (n=31) as compared to recipients of grafts from related donors (n=26).

In a recent retrospective study by the EBMT, reduced intensity condition (RIC) was compared to myeloablative conditioning.[12] A dose of melphalan less than 140 mg/m^2, a busulfan dose of 8 mg/kg or less and a cyclophosphamide dose of less than 120 mg/kg was considered to be reduced intensity. If total body irradiation was used, a dose of radiation less than 6 Gy or up to 6 Gy fractionated was accepted as RIC. With this definition, RIC was associated with lower non-relapse mortality but a higher relapse rate compared to myeloablative conditioning. The progression-free survival was superior with myeloablative conditioning but there

was no significant different in overall survival. Both ATG and alemtuzumab were associated with a higher relapse/progression rate, and alemtuzumab in addition with poorer progression-free and overall survival rates. It has to be pointed out that this was not a randomized study and the patients were often in an advanced stage of disease. The RIC regimens varied greatly and the definition of RIC may have included too intensively treated patients. Also, the patients who received RIC were older than those given myeloablative regimens. This may be the reason why transplant-related mortality was higher than in later studies comparing RIC with autologous transplants.

Prospective studies comparing reduced intensity condition transplants and autologous transplantation

Autologous stem cell transplantation, either single or in tandem, is the standard method for treating patients with multiple myeloma up to 65-70 years of age. Autologous transplantation is usually performed after an induction period using combination therapies such as VAD (vincristine, doxorubicin and dexamethasone) or, recently, combinations including bortezomib. The conditioning regimen is usually 200 mg melphalan/m^2. There are now five ongoing or closed prospective studies comparing RIC transplants following a first autologous transplant to autologous transplants – single or in tandem (Tables 1 and 2). These studies are based on so-called genetic randomization, i.e. patients with an HLA-identical sibling are offered a RIC allotransplant following the autologous transplant, while other patients receive either one or two autologous transplants. The first published study, by the *Intergroup Français de Myélome* (IFM),[13] included 65 patients in the autologous-allogeneic group, and 219 patients in the autologous-autologous group. Based on an intention-to-treat analysis, there was a significantly better median overall survival in the autologous-autologous group than in the autologous-allogeneic group. If only those patients who actually received the autologous-allogeneic transplant (46 patients) or tandem autologous transplant (166 patients) were analyzed, there was still a significantly superior overall survival in the tandem autologous transplant group. In this study, only patients under 65 years of age were included, their serum $\beta_2$microglobulin concentration had to be > 3 mg/L and they had to have deletion of chromosome 13. The RIC was busulfan + fludarabine and ATG. The result of this study discouraged the performance of allotransplants rather than autotransplants. However, in parallel there were four other ongoing studies. One of them, published by Bruno *et al.*[14], showed a superior overall survival for patients who underwent autologous-allogeneic transplantation. In this study, 245 patients were included at diagnosis. HLA typing was performed in 162 and 80 of these had an HLA-identical sibling donor while the other 82 patients did not and comprised the control group. However, for various reasons only 58 patients completed the autologous-allogeneic transplants and 46 the tandem autologous transplants. Whether analyzed according to the intent-to-treat, i.e. HLA typing had been performed, or based on actual treatment administered, there was a significant advantage of having an identical sibling or undergoing an auto-allotransplantation, respectively. It is interesting to note that the deviation in the survival curves to the advantage of the autologous-allogeneic regimen was seen only after about 2 years of follow-up. Thus, the major advantage was long-term survival in the autologous-allogeneic

Table 1. Patients and transplant characteristics in five prospective studies comparing RIC allogeneic transplants (allo) with autologous transplants (auto).

Group/Author	*Inclusion criteria*	*Conditioning for RIC-allotransplantation*	*Study design*
IFM Garban *et al.* 2006[13]	High – risk (high β_2 microglobulin, del13)	Fludarabine/busulfan/ATG	Auto/Allo *vs.* Auto/Auto
HOVON Lokhorst *et al.* 2007[16]	Patients < 66 years	TBI 2 Gy	Auto/Allo *vs.* Auto/ Maintenance
Italian Group Bruno *et al.* 2007[14]	All patients	TBI 2 Gy	Auto/Allo *vs.* Auto/Auto
PETHEMA Bladé *et al.* 2008[15]	Patients < 70 years No CR/nCR after 1st Auto	Melphalan/ Fludarabine	Auto/Allo *vs.* Auto/Auto
EBMT Björkstrand *et al.* 2008[17]	Patients < 70 years	TBI 2 Gy/Fludarabine	Auto/Allo *vs.* Auto or Auto/Auto

CR: complete remission; nCR: near complete remission; TBI: total body irradiation.

Table 2. Results of three closed studies and two interim analyses comparing tandem autologous/RIC allotransplantation versus autologous transplantation.

Group/Author	*N. of patients RICallo/Auto*	*CR rate (%)*	*EFS months (median)*	*OS months (median)*
IFM Garban *et al.* 2006[13]	46/166	62.2 *vs.* 51 (CR+VGPR) (*p*=NS)	31.7 *vs.* 35 (*p*=NS)	35 *vs.* 47.2 (*p*=0.07)
HOVON Lokhorst *et al.* 2007[16] Interim analysis	87 *vs.* 87	41 *vs.* 16	34 *vs.* 28	80% *vs.* 75% At 3 years
Italian Group Bruno *et al.* 2007[14]	80 *vs.* 82	55 *vs.* 26 (*p*=0.004)	35 *vs.* 29 (*p*=0.02)	80 *vs.* 54 (*p*=0.01)
Pethema Bladé *et al.* 2008[15]	25 *vs.* 85	40 *vs.* 11 (*p*=0.001)	PFS Not reached *vs.* 31 (*p*=0.08)	PFS Not reached *vs.* 58 (*p*=0.9)
EBMT Björkstrand *et al.* 2008[17] Interim analysis	108 *vs.* 248	52 *vs.* 41 (*p*=0.15)	PFS 28 *vs.* 28 (*p*= 0.87)	62% *vs.* 62% at 5 years (*p*=0.42)

CR: complete remission; VGPR: very good partial response; EFS, event-free survival; OS: overall survival; PFS: progression-free survival.

group. Patients were followed up to 84 months post-transplant. A third study was recently presented by the PETHEMA Group.[15] Only those patients who did not enter complete remission or near complete remission at the first autologous transplantation were included in the comparison between autologous-autologous and autologous-allogeneic transplantation. One hundred and ten patients had a second transplant, 25 of them a RIC-allogeneic transplant. Although, this was a relatively small series, there was no significant difference in event-free survival or overall survival between the autologous-RIC-allogeneic transplant recipients and the patients undergoing tandem autologous transplants, the shape of the curves being similar to those in the study by the Italian group.[14] The curves of the allogeneic RIC transplant recipients deviated at around 2 years after transplant to become horizontal, and the *p* value was 0.08. A fourth study by the HOVON Group, was recently presented[16] but the final analysis has not yet been made. At the interim analysis at 36 months of follow-up there was no significant difference between the groups that received autologous-RIC allogeneic transplants or tandem autologous transplants in event-free survival (median 34 months and 28 months, respectively) or overall survival (80% and 75%, respectively) at 36 months. An interim analysis of a fifth study – an EBMT study[17] – was recently presented with somewhat different inclusion criteria. Previously untreated patients received VAD or VAD-like induction treatment, and had a response status of at least stable disease (i.e. complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling then proceeded to RIC-allogeneic transplantations, while those without a matched sibling received no further treatment or a second autologous stem cell transplant (if treated within a tandem program). With these criteria, 356 patients were included, and the median follow-up is 3.5 years. One hundred and eight patients were allocated to the RIC-allogeneic transplant group and 248 to the autologous transplant group. Of the patients allocated to the allogeneic group, 98 received a RIC-allogeneic transplant. As of now, there is no significant difference in progression-free or overall survival between the double autologous and autologous-RIC allogeneic transplant recipients. However, the follow-up is too short for firm conclusions to be drawn and the study in still ongoing. Of particular interest, however, is that in patients with the del(13) chromosome abnormality the response rate is significantly higher and the relapse rate significantly lower with the autologous-allogeneic strategy. At 5 years, 68% of patients with this abnormality are alive, and 55% in the tandem autologous transplant group (p=0.075).

An important variable in these four studies is the conditioning regimen. Only the IFM used ATG in the conditioning regimen. Fludarabine was also used in the IFM study and in the studies by PETHEMA and EBMT. The Italian and HOVON studies used only 2 Gy total body irradiation without immunosuppression i.e. the original Seattle regimen. Thus, it appears that for the long-term outcome it may be better not to use additional immunosuppression such as fludarabine and ATG. However, this has yet to be demonstrated in further prospective studies.

Source of stem cells: peripheral blood or bone marrow

The great majority of allogeneic transplants recorded in the EBMT registry are now performed with peripheral blood stem cells. Recently, an analysis was made of 1,667 patients who had received a first allogeneic transplant from an HLA- identical sibling donor for multiple myeloma from 1994 to 2003 and had been reported to the EBMT database. Of these, 1,179 patients had received peripheral blood stem cells and 488 bone marrow. As shown previously, the engraftment rate was more rapid with peripheral blood stem cells irrespective of whether RIC or myeloablative conditioning was used. Otherwise, there was no significant difference in non-relapse mortality, relapse rate or response to treatment dependent on the source of stem cells. The conditioning regimen was, however, an important factor, i.e. transplant-related mortality was higher with myeloablative conditioning irrespective of whether the graft source was peripheral blood stem cells or bone marrow and the relapse rate was lower. Overall, chronic GVHD was more frequent with peripheral blood stem cells than with bone marrow, while the incidence of acute GVHD was similar. In a multivariate analysis, the higher rate of chronic GVHD disease did not translate into any detectable difference in relapse rate dependent on the cell source. Thus, even if there are minor differences in some parameters, the use of peripheral blood stem cells or bone marrow results in similar overall survival.

How could the results of allogeneic transplantation be improved?

Strategies to improve outcome with allogeneic transplantation are not obvious, although there are several different possibilities, e.g. including new drugs in the conditioning regimens or pre-transplant, use of donor lymphocyte transfusions post-transplant, and use of natural killer (NK) cells post-transplant either pre-emptively or at early signs of relapse. Also, unrelated donors selected by high-resolution HLA typing, may be as good as or even better than related donors for long-term outcome with RIC allotransplantation and KIR ligand donor-recipient mismatched transplants or KIR ligand mismatched donor lymphocyte transfusions may be alternatives to reduce relapse rate.[18]

Donor lymphocyte transfusions

Donor lymphocytes transfusions, used to treat relapse following allogeneic transplantation, may induce responses, which can last for more than 2 years, in about 30% of relapsed patients. These transfusions frequently cause GVHD, and the response rate and duration are often associated with chonic GVHD.

In a multinational European multicenter study[19] escalating dosages of donor lymphocytes were studied in 63 patients who were refractory to or relapsed after RIC allogeneic transplantation. Twenty-four patients responded – 12 of whom had a complete response. Overall survival was 23.6 months from the time of the

donor lymphocyte infusions, and in responders the progression-free survival was 27.8 months. Major toxicities were acute GVHD (38.1%) and chronic GVHD (42.9%), and seven patients (11.1%) died from treatment-related causes.

This study illustrates that although responses of significant duration can be obtained with donor lymphocyte infusions, GVHD is rarely separated from the GVM effect. Recently it has been shown that KIR ligand mismatched transplants my reduce relapse rates without an obvious increase in GVHD – and could perhaps be explored further for both transplants and donor lymphocyte transfusion.

Including immunosuppression in the conditioning regimen

In a study in the present issue of the journal Ayuk *et al.*[20] used ATG (Fresenius®) in the conditioning method in an attempt to improve results. The conditioning regimen consisted of melphalan 100-150 mg/m^2 administered intravenously on days -3 and -2, and fludarabine (median total dose 120 mg/m^2, range 90-180 mg/m^2) given on days -7 to -3. Seventy-nine (57%) of these patients also received ATG while 59 patients (43%) did not. There was less acute GVHD grade III-IV, and chronic GVHD in the ATG group. Also, the response rate was higher in the ATG group and there was a trend for improved event-free survival at 3 years. There was, however, no significant improvement in overall survival.

These results must be interpreted with caution. As mentioned previously, Crawley *et al.*[12] found a significantly poorer survival when alemtuzumab or ATG was included in the conditioning regimen. A higher relapse rate was seen with both agents. Other studies have also reported higher relapse rates among patients in whom ATG has been included in the conditioning.[21] As suggested by Kröger *et al.*, these differences may be related to the source of ATG as well as to its dosage. They used ATG Fresenius® at high dosages (up to 90 mg/kg) claiming that this might produce an antimyeloma effect, while other studies – including the one by Crawley *et al.* – frequently use thymoglobuline at dosages of 8 – 12.5 mg/kg. ATG-Fresenius® is derived from the human Jurkart T-cell line, while thymoglobuline is an antithymocyte globulin derived from human thymocytes, which may also explain differences in effects. It must, however, be pointed out that among the prospective studies described above the best results were obtained by Bruno *et al.*[14] who did not include any immunosuppression in the conditioning regimen, while the worst ones were obtained by Garban *et al.*, who used high doses of ATG. Thus further studies are needed to draw firm conclusions on the value of ATG in conditioning regimens.

Post- or pre-transplant use of new targeted drugs

Bortezomib is a proteosome inhibitor that blocks the activation of NF-κB, and is an important mediator of myeloma cell survival. It seems that bortezomib inhibits alloreactive mixed lymphocyte responses, increasing T-cell-dependent killing of tumor cells.[22] In a murine model bortezomib administered together with an allogeneic stem cell transplant prevented GVHD while preserving the graft-versus-tumor effect. There are, however, other conflicting reports claiming increased GVHD. Thus, although bortezomib is now one of the most effective drugs used in the treatment of multiple myeloma, its place in association with allogeneic stem cell transplantation is not clear.[23] Probably it can be used in cases of progression and relapse following allogeneic transplantation and also in the induction regimen, but it is unclear whether it should be used in close association with transplantation or in association with donor lymphocyte infusions.

Lenalidomide is an immunmodulatory drug that has stimulatory effects on host anti-tumor T cells and NK cells. In a recent study[24] lenalidomide was given to 16 patients with end-stage myeloma who relapsed after allogeneic transplantation: the response rate was 91% and three of the 16 patients had a complete response. Only three patients developed acute GVHD and chronic GVHD was improved in two patients. It is, therefore, possible that lenalidomide is particularly valuable in relapses following allogeneic transplantation. The NK stimulatory effect could be a rationale for trying to expand NK cell treatment[25] in association with lenalidomide in relapse following allogeneic transplantation.

Natural killer cells to modulate GVHD and increase the antimyeloma effect

There is experimental evidence that NK cells have an antimyeloma cell effect.[26] Recent studies in a mouse myeloma model have shown improved survival following NK cell treatment when used together with interleukin-2. Furthermore, *in vitro* studies have shown that expanded human NK cells can kill human myeloma cells.[25] In the allogeneic setting the administration of NK cells has been related to increased efficacy and improved survival of patients with acute leukemia transplanted with haploidentical T-cell-depleted allogeneic stem cells.[27] Thus expanded NK cells may be used to treat relapse/progression following allogeneic transplantation.

Conclusions

Myeloablative allogeneic transplantation in multiple myeloma is hampered by a high transplant-related mortality, and is presently not generally recommended except in clinical trials of selected groups of patients and with new approaches, perhaps in combination with novel drugs or other therapies. RIC allogeneic transplantation may be superior to autologous transplantation – single or tandem – but results are still controversial. Alemtuzumab appears to be contraindicated as part of conditioning regimens but other immunosuppressive agents may be used, although preferentially in clinical trials since the role of ATG and fludarabine is still unclear. New drugs, such as bortezomib, and novel cell therapies such as NK-cell treatment in association with RIC allogeneic transplantation, are potential strategies for improving results. Further studies are needed to determine the right place for these possible approaches.

Dr. Gahrton's studies on multiple myeloma were supported by the Swedish Cancer Fund and the Cancer Society of Stockholm.

References

1. Gahrton G, Ringden O, Lonnqvist B, Lindquist R, Ljungman P. Bone marrow transplantation in three patients with multiple myeloma. Acta Med Scand 1986;219:523-7.
2. Gahrton G, Tura S, Ljungman P, Belanger C, Brandt L, Cavo M, et al. Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. N Engl J Med 1991;325:1267-73.
3. Björkstrand BB, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. Blood 1996;88:4711-8.
4. Gahrton G, Iacobelli S, Apperley J, Bandini G, Björkstrand B, Bladé J, et al. The impact of donor gender on outcome of allogeneic hematopoietic stem cell transplantation for multiple myeloma: reduced relapse risk in female to male transplants. Bone Marrow Transplant 2005;35:609-17.
5. Hambach L, Spierings E, Goulmy E. Risk assessment in haematopoietic stem cell transplantation: minor histocompatibility antigens. Best Pract Res Clin Haematol 2007;20: 171-87.
6. Gahrton G, Svensson H, Cavo M, Apperly J, Bacigalupo A, Björkstrand B, et al. Progress in allogenic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983–93 and 1994–8 at European Group for Blood and Marrow Transplantation centres. Br J Haematol 2001;113: 209-16.
7. Corradini P, Voena C, Tarella C, Astolfi M, Ladetto M, Palumbo A, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. J Clin Oncol 1999;17: 208-15.
8. Corradini P, Cavo M, Lokhorst H, Martinelli G, Terragna C, Majolino I, et al. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. Blood 2003;102:1927-9.
9. Maloney DG, Molina AJ, Sahebi F, Stockerl-Goldstein KE, Sandmaier BM, Bensinger W, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood 2003;102:3447-54.
10. Georges GE, Maris MB, Maloney DG, Sandmaier BM, Sorror ML, Shizuru JA, et al. Nonmyeloablative unrelated donor hematopoietic cell transplantation to treat patients with poor-risk, relapsed, or refractory multiple myeloma. Biol Blood Marrow Transplant 2007;13:423-32.
11. Kröger N, Shimoni A, Nagler A, et al. Current status and perspectives of dose-reduced conditioning followed by related and unrelated stem cell transplantation. Haematologica 2005;90:47.
12. Crawley C, Iacobelli S, Bjorkstrand B, Apperley JF, Niederwieser D, Gahrton G. Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. Blood 2007;109:3588-94.
13. Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, Yakoub-Agha I, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-80.
14. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-20.
15. Bladé J, Rosinol L, Pérez-Simon J, Sureda A, De La Rubia J, De Arriba F, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced - intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma [abstract]. Haematologica 2008;93(s1):166.
16. Lokhorst H, Mutis I. Allogeneic transplantation and immune interventions in multiple myeloma. In: Green T, Salles G, Boregaard N, eds. Hematology Education: the education programme for the annual congress of the European Hematology Association 2008; 2:106-14.
17. Björkstrand B, Iacobelli S, Hegenbart U, et al. Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning allogeneic SCT with identical sibling donor in previously untreated multiple myeloma: preliminary analysis of a prospective controlled trial by the EBMT. Bone Marrow Transplant 2008;41:S38.
18. Kröger N, Shaw B, Iacobelli S, Zabelina T, Peggs K, Shimoni A, et al. Comparison between antithymocyte globulin and alemtuzumab and the possible impact of KIR-ligand mismatch after dose-reduced conditioning and unrelated stem cell transplantation in patients with multiple myeloma. Br J Haematol 2005;129:631-43.
19. van de Donk NW, Kröger N, Hegenbart U, Corradini P, San Miguel JF, Goldschmidt H, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant 2006;37:1135-41.
20. Ayuk F, Perez-Simon J, Shimoni A, Shimoni A, Sureda A, Zabelina T, et al. Clinical impact of human Jurkat T-cell-line-derived antithymocyte globulin in multiple myeloma patients undergoing allogeneic stem cell transplantation. Haematologica 2008;93:1343-50.
21. Remberger M, Mattsson J, Svahn B, Ringdén O. Using reduced intensity conditioning and HLA-identcal sibling donors, antithymocyte globulin increases the risk of relapse, which can be overcome by a high stem cell dose. Submitted for publication 2008.
22. Sun K, Welniak LA, Panoskaltsis-Mortari A, O'Shaughnessy MJ, Liu H, Barao I, et al. Inhibition of acute graft-versus-host disease with retention of graft-versus-tumor effects by the proteasome inhibitor bortezomib. Proc Natl Acad Sci USA 2004;101:8120-5.
23. Mateos-Mazon J, Perez-Simon JA, Lopez O, Hernandez E, Etxebarria J, San Miguel JF. Use of bortezomib in the management of chronic graft-versus-host disease among multiple myeloma patients relapsing after allogeneic transplantation. Haematologica 2007;92:1295-6.
24. Lokhorst H. Allogeneic transplantation in multiple myeloma. Haematologica 2007;92:52-4.
25. Alici E, Sutlu T, Björkstrand B, Gilljam M, Stellan B, Nahi H, et al. Autologous antitumor activity by NK cells expanded from myeloma patients using GMP-compliant components. Blood 2008;111:3155-62.
26. Alici E, Konstantinidis KV, Sutlu T, Aints A, Gahrton G, Ljunggren HG, Dilber MS. Anti-myeloma activity of endogenous and adoptively transferred activated natural killer cells in experimental multiple myeloma model. Exp Hematol 2007;35:1839-46.
27. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 2002;295:2097-100.