RESULTS OF ALLOGENEIC BLOOD STEM CELL TRANSPLANTATION IN THE TREATMENT OF MULTIPLE MYELOMA WITH PARTICULAR FOCUS ON RELAPSE THERAPY AFTER TRANSPLANTATION

Abstract

This retrospective study investigated 69 patients with multiple myeloma who received allogeneic stem cell transplantation (SCT) at the Regensburg University Hospital between 2000 and 2013. Data from two patients with second transplantations from different donors was also included. Hence, 71 allogeneic SCT were analysed, of which ultimately 46 patients were treated after allogeneic SCT due to relapse.

The median progression-free survival after allogeneic SCT for the whole group was 10.2 months and overall survival was 51.1 months. Median overall survival was 52.1 months in patients with relapse after allogeneic SCT and 10.1 months in patients with no relapse. Median overall survival after diagnosis of a relapse after allogeneic SCT was 50.2 months. After achieving complete remission (CR) as a result of a treatment for relapse after allogeneic SCT, the median disease-free survival was 35.0 months. In contrast, the median disease-free survival in patients with very good partial response after allogeneic SCT and subsequent treatment for relapse was only 6.7 months. These results indicate that unlike other diseases, long-term control is possible even in the case of relapse after allogeneic SCT, in particular in patients who achieve CR.

Treatment-related mortality occurred in 22.1 % of patients following allogeneic SCT. Almost half of these patients died due to acute graft-versus-host-disease (GvHD) and infection. Treatment-related mortality up to day 100 was 9.0 %.

Multivariate analysis revealed that a positive factor for significantly longer progression-free survival after allogeneic SCT was a second CR at the time of the allogeneic SCT compared to later transplantations (> second CR, > first partial response (PR), stable disease, progressive disease). Transplantations in the first CR showed no advantage compared to those in first PR in terms of longer progression-free survival. These results highlight that for longer progression-free survival, at least one PR at the time of the allogeneic SCT appears to be particularly important, with an advantage for patients who receive transplantation no later than during second remission. However, reliable conclusions are limited by the small number of patients in the collective. Further, the analysis reveals the most positive independent factor for significantly longer progression-free survival is a primary schedule autologous/allogeneic SCT compared to allogeneic SCT in relapse after autologous SCT. Moreover, we confirmed only in univariate analysis but compared with other studies we identified as relevant positive

factors for longer progression-free survival at most two previous therapies before allogeneic SCT and the occurrence of chronic GvHD, in particular in moderate to severe cases.

Compared to chemotherapy alone, chemotherapy in combination with donor lymphocyte infusion (DLI) did not achieve significantly better progression-free survival. Patients who developed (mostly chronic) GvHD as a consequence of chemotherapy with DLI showed higher rates of response. In particular, almost all patients who achieved CR experienced chronic GvHD.

Compared to the overall collective, a chronic GvHD after allogeneic SCT did not lead to a longer progression-free survival and overall survival; however, even when examined only in univariate analysis, chronic GvHD appeared to be a significant positive factor for longer progression-free survival.

Of all the substances administered during relapse after allogeneic SCT, the best response rates and the longest progression-free survival was achieved with lenalidomide. Compared to treatment with lenalidomide alone, the combination of lenalidomide and DLI resulted in greater response rates and longer progression-free survival. The toxicity rate under lenalidomide was relatively low but the incidence of GvHD was quite high.

Likewise, treatment with bortezomib resulted in good response rates with a significant increase in the CR rate and extension of progression-free survival achieved with additional DLI. The incidence of GvHD was low but the toxicity rate was highest amongst all the substances administered at 64.0 %.

Thalidomide monotherapy with no additional DLI resulted in low incidence of GvHD and moderate toxicity rate while achieving response rate as good as with bortezomib. Thalidomide in combination with DLI resulted in no treatment response but very high incidence of GvHD. Because of the small number of cases, the extent to which additional DLI in relapse after allogeneic SCT actually plays a role cannot be determined.

With low rates of toxicity and GvHD, interferon alpha proved to be especially effective in maintenance therapy. In almost all cases, the previous remission condition could be significantly prolonged without improving the remission status. Only one patient with myeloma progression achieved long-term remission using interferon alpha but this was accompanied by ongoing active moderate to severe chronic GvHD. Additional DLI showed no better effects but higher incidence of GvHD.

In terms of response rates and progression-free survival, biomodulatory metronomic chemotherapy and a therapy with bortezomib, cyclophosphamide, dexamethasone (BDC) and cyclophosphamide, adriamycin, dexamethasone (CAD) were with moderate to low toxicity rates inferior to the new substances (lenalidomide, bortezomib, thalidomide). Bendamustine and melphalan (low dose) showed no response and should be considered palliative therapy options with low toxicity rates. The extent to which pomalidomide shows effects in relapse after allogeneic SCT could not be estimated due to low numbers of cases.

Compared to other studies that in some cases showed better results from relapse therapy after allogeneic SCT, the patients in this analysis were already in a more advanced stage of disease and overall had undergone more previous treatments. In addition, the patient collectives in other studies were generally small and not all patients were in progression at the beginning of therapy. The results of this study indicate that even with a wide range of previous therapies, patients in relapse after allogeneic SCT showed high response rates between 50.0 % and 81.9 % and long progression-free survival periods between 8.0 and 14.9 months with an overall moderate side effect profile, especially through the use of new substances. Additional DLI may in part enhance the immunomodulatory effect and thus the graft-versus-myeloma effect, depending on the development of chronic GvHD. Subsequent maintenance therapy with interferon alpha can significantly extend the progression-free survival period.

The results also indicate that immunological control of the disease is associated with chronic GvHD and at the same time is key for achieving long-term remission. In terms of the optimal timing of the SCT, the results support the use of allogeneic SCT following the first autologous SCT as a part of the primary therapy or no later than in the second remission. A CR after allogeneic SCT is key for achieving long-term remission and must therefore also be viewed as an important prerequisite for long-term remission. However, long-term remission that is just as long as in patients after the first CR after allogeneic SCT, with the prospect of a curative effect, can also be achieved in patients in relapse after allogeneic SCT.