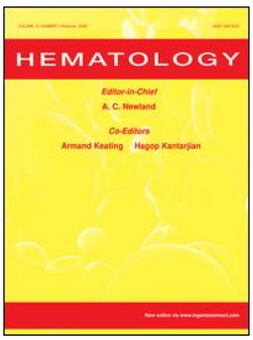

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MULTIPLE MYELOMA

Role of stem cell transplantation in myeloma

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Both autologous and allogeneic hematopoietic stem cell transplantation are used in the treatment of patients with multiple myeloma. Two randomized prospective studies have shown that autologous transplantation is superior to conventional chemotherapy at least for patients younger than 60 – 65 years of age [1,2]. Median survival has improved from 42 and 44 months to 54 and 57 months respectively. Prognostic factors have been extensively analyzed and many are similar to those with conventional chemotherapy. Favorable prognosis is seen in younger patients, patients lacking certain chromosomal aberrations (-13), those that are not heavily pretreated and those that are responsive to previous treatment. Tandem autologous transplantation appears to be superior to single transplantation, at least in patient that do not enter complete hematologic remission after the first transplantation [3]. The most favorable time for the second transplant seems to be within 6 – 12 months [4]. Attempts to reduce relapse and progression by reducing the tumor load in the autologous cell suspension through CD34+ cell selection have been unsuccessful [5,6]. Molecular remissions are rare events following autologous transplantation and patients do not seem to be cured [7].

Allogeneic transplantation may have the potential to cure a fraction of the patients [8]. Molecular remissions are more frequent than with autologous transplantation [9]. However, conventional high dose myeloablative conditioning transplants are hampered by about 30–35 % transplant-related mortality (TRM), although this mortality has been reduced in transplants performed from 1994 as compared to those performed before 1994, mainly due to earlier transplantation and more effective treatment of bacterial, fungal and viral infections [10]. Median overall survival was 50 months in later transplants. Favourable prognostic factors for myeloablative transplantation are low age, low β-2-microglobulin (β-2-m), stage I at diagnosis, responsiveness to previous treatment and only one treatment regimen before transplantation. Recently it was shown that although the female to female combination has the best outcome the relapse rate in males with a female donor is significantly lower than in males with a male donor, compensating for the higher transplant related mortality in this combination [10]. Procedural factors play a role for outcome, but documentation is poor. The most frequently used conditioning regimen for myeloablation, cyclophosphamide 60 mg $kg^{-1} \times 2$ plus 10 Gy total body irradiation with lung shielding to 9 Gy has not been surpassed by numerous other regimens reported to the EBMT registry.

A recent EBMT registry study indicates that reduced intensity nonmyelablative (NMA) regimens result in lower TRM but a higher relapse rate than with myeoablative regimens [11]. The higher relapse rate might be counteracted by a previous autologous transplantation and later donor lymphocyte transfusions. EBMT is presently running a prospective study comparing tandem autologous-NMA allogeneic transplantation to autologous transplantation alone based on the availability of an HLA matched sibling donor. Scheduled donor lymphocyte transfusions are given post transplantation dependant on response or recurrence. The safety analyses indicate 11% early TRM following the NMA transplantation.

In summary, autologous transplantation is the golden standard for the treatment of most patients with multiple myeloma. Tandem transplantation may be superior to single transplantation in younger patients that do not enter complete remission after the first transplant. Non myeloablative allogeneic transplantation reduces transplant related mortality

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compared to myeloablative transplantation but the relapse rate is higher and overall survival appears not clearly affected. It should still preferentially be performed in controlled trials. Myeloablative transplantation may be an option for selected younger patients with stage IIIA disease, preferentially for younger women that have an HLA matched female sibling donor. Patients that have been responsive to previous conventional treatment and have received only one treatment regimen before the transplant are the best candidates. However some patients that have not responded or have relapsed after autologous transplantation may be offered an allogeneic transplant if their general condition is otherwise good.

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