MULTIPLE MYELOMA

Stem cell transplantation in multiple myeloma

BO BJÖRKSTRAND

Institutet at Huddinge Hospital, Stockholm, Sweden

Single autologous transplantation

High-dose treatment (HDT) with autologous stem cell transplantation (ASCT) has been shown to increase survival and time to progression in multiple myeloma (IMM) compared with conventional chemotherapy. In the French IFM90-study [1], 200 patients were randomised to receive prolonged standard treatment with i.v. combination chemotherapy, or a short phase by induction treatment with the same regimen, followed by high-dose melphalan + TBI and autologous bone marrow transplantation (ABMT). Median survival was significantly better in the ABMT-arm, +60 months, vs. 37 months in the chemotherapy arm, and also event-free survival was superior, 27 months vs. 18 months. These differences are sustained in a long term follow-up, where actuarial survival at 7 years was 43% and 25%, and EFS was 16% and 8% in the ABMT- and chemotherapy arms, respectively. However, these latter differences were only observed in patients under the age of 60 at the time of inclusion in the study, while there was no benefit in older patients [1a]. Similar results have been demonstrated in a more recently published study from the British MRC [2]: 401 patients were randomized to receive either standard chemotherapy (cVAMP) or cVAMP followed by high-dose melphalan and autologous SCT. Median overall survival (OS) was significantly superior in the ASCT-arm — 51 months — compared with 42 months in the cVAMP-group. The difference was most pronounced in patients with a high beta-2-microglobulin (β-2-m) value at diagnosis, i.e. with a poorer prognosis.

Tandem autologous transplantation

During the last 10 years, there have been indications from non randomized trials and treatment programs that repeated HDT with ASCT, i.e. tandem or double transplantation, can further improve these results [3–5]. These data have been confirmed in recent randomized trials. In the French IFM94-study [6], 399 previously untreated patients were randomized at diagnosis to receive either single or double ASCT following induction treatment. Conditioning in the single transplant arm and for the second transplant in the double transplant arm was melphalan 140 mg/sqm plus TBI 8 Gy total dose in 4 fractions. For the first transplant in the double transplant group, melphalan 140 mg/sqm was used. The rate of CR or VGPR was 49% and 63% in the single and double transplant groups, respectively ($P=0.10$). Median OS was prolonged with 10 months in the double transplant group (58 months, vs. 48 months for the single transplant group, $P=0.01$). The probability of survival at 7 years was 21% vs. 42% and of EFS 10% vs. 20% for the single and double transplant groups, respectively. In an Italian randomized study of 386 patients conditioning for the first transplantation was melphalan 200 mg/sqm and for the second melphalan 120 mg/sqm plus busulfan 12 mg/kg. Median OS was 62 vs. 74 months and median EFS 21 vs. 31 months for the single and double transplant groups, respectively [7]. In contrast to these results, another French randomized study in 230 patients has failed to demonstrate a significant benefit of the double transplant procedure [8]. Concerning the optimal timing of the two transplants, an EBMT registry study has recently demonstrated that the second transplant should preferably be performed before relapse and within 6 to 12 months of the first transplantation [9].

It can be concluded that tandem autologous transplantation seems to improve survival with about one year compared with single autografting, and that it is beneficial to perform the second transplant within a short interval after the first, before disease progression.
Allogeneic stem cell transplantation with full dose conditioning

Allogeneic stem cell transplantation (SCT) with full-dose conditioning has been used in MM for almost 20 years. The treatment results have been hampered by a very high transplant-related mortality (TRM) rate of 25–50%, and furthermore, the curative potential can be questioned since late relapses after several years do occur [10,11], although molecular remissions can be achieved in a way not seen after autologous transplantation [12]. In 1996, the EBMT Myeloma Registry performed a retrospective analysis comparing 189 allogeneic transplant patients with 189 case-matched autologous transplant controls [10]. The results were consistent with previous surveys, with a significantly better survival for the autotransplant group (median survival after transplantation 34 months, vs. 18 months in the allogeneic group). Relapse rate was significantly higher in the autotransplant group (70%) vs. 50% for the allogeneic transplant patients. This difference did not however compensate for the large difference in TRM—41% in the allogeneic vs. 13% in the autologous transplant group, respectively—which was the reason for the poorer survival of the allogeneic transplant patients. In spite of extensive analyses of different prognostic subgroups, no category of patients could be identified where allogeneic transplantation would be more favorable than autologous, although no survival difference was seen in female patients.

A more recent EBMT study compared 225 allogeneic bone marrow transplants performed during 1994–98 with 339 patients transplanted during 1983–93 [11] This analysis demonstrated a decrease in TRM, with a reduction of total TRM from 50 to 30%, and early mortality from 30 to 20%. This resulted in an improvement in outcome, with an actuarial survival of about 50% at 4 years after transplantation, compared to about 30% in the previously transplanted group of patients. Still, although improved, TRM is unacceptably high.

Based on these and other studies with similar results, allogeneic SCT with full dose conditioning can not be recommended, not even for younger patients, until the lethal complications can be handled more effectively.

Allogeneic stem cell transplantation with reduced intensity conditioning

Based on the high toxicity of allogeneic SCT with full dose conditioning, it is not surprising that MM is one obvious target disease for reduced intensity-conditioning (RIC) or non-myeloablative allogeneic (NMA) transplantation, also called ‘mini-transplantation’ where the rationale is to utilize the antitumor effect of the graft-versus-myeloma reaction, while reducing the treatment-related complications of high-dose conditioning [13,14]. In a retrospective survey of 256 patients reported to the EBMT myeloma registry, TRM was about 24%, but only 13% in low-risk patients, i.e. mainly patients transplanted upfront as a part of first-line treatment [15]. One treatment rationale frequently used is to induce maximal cyto-reduction by induction treatment, HDT (mainly high-dose melphalan) and ASCT, followed by consolidation with with RIC allogeneic transplantation and if necessary, also infusion of alloreactive donor T-lymphocytes (DLI). This strategy has been used in a number of phase II-studies, of totally 124 patients [16–19]. The conditioning regimens have been variable and of low or intermediate cytotoxic intensity, and have included fludarabine, low dose TBI, melphalan, cyclophosphamide and ATG. Transplant-related mortality has varied between 4–13% in previously untreated or less treated patients, and about 25% in relapsed and/or heavily pretreated patients. OS and EFS at 2–3 years was 50–100% and 30–60%, respectively in less-treated or relapsed but chemosensitive patients. The incidence of acute and chronic GVHD varied between 10–60% and 40–65%, respectively. As for controlled prospective trials, preliminary data from one study have been presented [20]. Two hundred and eighty-four previously untreated patients have been included, all receiving VAD induction treatment and high-dose melphalan (200 mg/sqm) with ASCT. For inclusion, the patients needed to have poor prognosis criteria with respect to abnormal karyotype and high β-2-m. Sixty-four patients with an HLA-identical sibling donor then received an RIC allogeneic transplantation, while 220 patients with no available donor were randomized to no further treatment or to receive a second autograft after high-dose melphalan 220 mg/sqm. The allogeneic transplant conditioning regimen consisted of fludarabine, low dose busulfan and ATG. Median follow-up time from diagnosis is 23 months (9–44). At 4 years, the probability of survival—on an intention-to-treat basis—was 40% in the autologous vs. 30% in the allogeneic transplant arms (P=0.36), and EFS 20% vs. 15% (P=0.70). When comparing the patients who actually received their planned transplants — 46 in the allogeneic- and 166 in the autologous transplant group, the corresponding results for survival was 50% for the autologous and 35% for the allogeneic transplant patients (P=0.09), i.e. a trend for better outcome after autologous SCT. EFS was essentially identical in both groups – about 18% at 4 years. Transplant-related mortality at 3 months after allogeneic transplantation in the 406 patients who completed all treatment was 6%.

In a retrospective registry study of the EBMT [21], 321 RIC allografts were compared with 196 allo-transplants with standard conditioning (SC). The transplants were performed during the same period...
of time, 1998–2002. No case matching was done, and
the groups were not completely comparable with
respect to prognostic factors. Median survival was
23 and 36 months ($P=N.S$) and PFS was 11 and 17
months ($P=N.S$) for the RIC and SC groups,
respectively. Non-relapse mortality at 2 years was
significantly higher for the SC group – 37% vs. 23%
for the RIC patients. The cumulative relapse inci-
dence at 3 years was higher in the RIC group, 54%,
compared with 26% in the group that received SC.

Allogeneic SCT with reduced intensity conditioning
is feasible, and TRM is low and acceptable in contrast
to SC. However, relapse rate seems to be higher, and
long-term outcome does not seem to be improved.
High-dose treatment and ASCT followed RIC allo-
genous transplantation is feasible, but preliminary
results from controlled prospective trials still do not
demonstrate a benefit in survival or freedom of
progression compared with single or tandem auto-
logous SCT, at least not in high-risk patients. Data
from other similar studies, like the EBMT study with
a similar design as the French trial but also including
patients without high-risk criteria, will be available in
the near future.

References

bone marrow transplantation and chemotherapy in multiple
4:S55.
348:1875–1883.
with autologous stem cell transplantation can induce mole-
cular remissions in multiple myeloma. Bone Marrow Trans-
(AT) with “total therapy” (TT) compared to standard
SWOG treatment (ST) for multiple myeloma (MM). Blood
349:2495–2502.
61.
high dose therapy (HDT) supported with autologous blood
stem cell (ABSC) transplantation using unselected or CD34-
enriched ABSC: results of a two by two designed randomized
multiple myeloma: clinical findings and methodological limita-
tions in a European Group for Blood and Marrow Transplanta-
versus autologous stem cell transplantation in multiple mye-
loma-a retrospective case-matched study from the European
Group for Blood and Marrow Transplantation. Blood 1996;
88:4711–4718.
peripheral blood stem cell transplantation for multiple mye-
loma: a comparison between transplants performed 1983–
allogeneic stem cell transplantation predicts a better relapse-
free survival in patients with multiple myeloma. Blood 2003;
multiple myeloma after allotransplantation using a nonmye-
loablative conditioning regimen and donor lymphocyte infu-
older patients with hematologic malignancies: replacing high-
dose cytotoxic therapy with graft-versus-tumor effects. Blood
2001;97:3390–3400.
allogeneic transplantation in myeloma-a report from the
[16] Badros A, et al. Improved outcome of allogeneic transplanta-
tion in high-risk multiple myeloma patients after nonmyelo-
by a dose-reduced allograft induces high complete remission
[18] Einsele H, et al. Follow-up of patients with progressive
multiple myeloma undergoing allotransplants after reduced-inten-
conditioning following cytoreductive autografts for the treat-
ment of patients with multiple myeloma. Blood 2003;102:
3447–3454.
[20] Harousseau, J-L. Preliminary results of the IFM9903 and
IFM9904 protocols comparing autologous followed by min-
iallogeneic transplantation and double autologous transplant
in high-risk de novo multiple myeloma. 10th International
[21] Crawley, C, et al. Reduced-intensity conditioning does not
improve survival compared to standard conditioning for
patients with myeloma. Bone Marrow Transplant 2005; 35:
S48.