

Review

Cure of myeloma: hype or reality?

A Fassas, J Shaughnessy and B Barlogie

Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Summary:

High-dose treatment (HDT) with autologous stem cell transplant(s) (ASCT) improved survival, when compared to standard treatment, in multiple myeloma patients. Although the superiority of HDT is clearly recognized by the medical community, what is less appreciated is the disproportionate benefit enjoyed (as a result of this approach) by various patient subgroups. As the clinical heterogeneity of myeloma can be currently traced to its underlying genetic features, prognostically different patient groups can be identified largely based on the presence of adverse cytogenetic abnormalities and high serum levels of lactate dehydrogenase at baseline (high-risk features). While HDT applied to high-risk patients leads to modest survival gains, the same treatment, as the backbone of a comprehensive approach, can be curative in a minority of low-risk patients. A third group of low-risk patients will enjoy rather prolonged (10-year) survival, interrupted, however, by responsive relapses. In a manner analogous to follicular lymphoma, this latter group may transform to a more aggressive disease, characterized by the new acquisition of adverse cytogenetic abnormalities. Improving the complete response rate in these patients, by integrating newer therapeutic agents, may increase their cure rate. Currently non-myeloablative, allogeneic transplants (and possibly proteasome inhibitors) are the most promising approaches for high-risk patients.

Bone Marrow Transplantation (2005) 35, 215–224.

doi:10.1038/sj.bmt.1704757

Published online 15 November 2004

Keywords: multiple myeloma; autologous transplant; allogeneic transplant; cure

There has been historically a nihilistic approach towards managing patients with multiple myeloma (MM). The disease is not immediately life-threatening (at least in the majority of patients) and mainly affects the elderly (median age at diagnosis 65 years) leading not uncommonly to severe functional limitations due to skeletal pains and spine

fractures, renal insufficiency and profound immunosuppression. Since palliation was viewed as a reasonable goal, it is not surprising that, for approximately three decades, the combination of melphalan and prednisone (MP) was the 'gold standard' of treatment despite its dismal record. The regimen led to a partial response (PR) rate of 50–60% (with a complete response (CR) rate <5%) and a modest median survival of 3 years.¹ Addition of other alkylating agents, anthracyclines and *Vinca* alkaloids to MP regimen did not improve survival, since the achieved dose intensity with the multiagent combinations did not lead to significantly more cytoreduction.² Escalating the dose of steroids, as in VAD (vincristine, doxorubicin, dexamethasone) regimen, produced rapid and marked cytoreduction in approximately 50% of patients relapsing after MP,³ but it did not increase the CR rate or prolong survival, when used upfront.⁴

Extrapolating from the treatment experience in acute leukemias, it was felt that *a sine qua non* for prolonging survival and possibly curing myeloma is the achievement of complete remission in a sizable fraction of patients. Intensification of treatment was therefore the next logical step. Melphalan was chosen due to its efficacy and its lack of significant toxicity (outside of bone marrow and mucous membranes). Three (all previously untreated) of nine myeloma patients who received a single high-dose melphalan (140 mg/m²) achieved biochemical and bone marrow CR.⁵ Since the first heroic trial (1983) by the late Tim McElwain (who did not support his patients with either stem cells or growth factors), HDT has evolved to the point that MM is currently the second most frequent indication for transplant in the US. The use of peripheral blood stem cells (instead of autologous bone marrow) with its associated faster hematologic recovery has led to a transplant-related mortality (TRM) of approximately 2–3%,⁶ similar to the mortality observed during the first 6 months of standard treatment in MM patients.^{4,7} Over the last 5 years, thalidomide was found to salvage one-third of patients relapsing after HDT⁸ and proteasome inhibitors have been brought to the clinic with encouraging results.⁹ These major advances in treatment have also been accompanied by improvements in supportive care, such as the use of bisphosphonates^{10,11} and erythropoietin¹² and the introduction of kyphoplasty and vertebroplasty.^{13,14}

There is currently plenty of evidence to support the conclusion that HDT with ASCT is superior to standard treatment in terms of CR rate, CR duration, event-free survival (EFS) and overall survival (OS).^{15–19} However,

Correspondence: Dr A Fassas, Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, 4301 W. Markham St., Little Rock, AR 72205, USA;
E-mail: FassasAthanasios@uams.edu
Published online 15 November 2004

(and unlike Hodgkin's disease, non-Hodgkin's lymphoma and germ cell tumors where HDT is widely considered curative for a subset of patients), the medical community has yet to accept the notion that cure is indeed possible in myeloma. Although cure might theoretically imply the total eradication of all malignant plasma cells (translated into uninterrupted CRs), an 'operational' definition of cure would be applicable in patients with stable monoclonal component levels for long time periods (translated into long EFS). Such patients ('operationally' cured) would resemble patients with chronic or acute leukemias in whom long-term survival is not affected by the persistent low-level detection of the relevant molecular marker.²⁰ We will try to challenge this 'no cure' notion by submitting that HDT, as backbone of a comprehensive treatment program, is curative in certain subsets of patients with multiple myeloma. Conversely, other patient subgroups will derive a relatively modest benefit from even the timely application of tandem autotransplants, which (albeit statistically superior to standard treatment) is clinically less pronounced. In a manner analogous to Ph+ acute lymphoblastic leukemia, achievement of CR is frequent in such patients; however, CR is not sustained. Novel therapeutic approaches, designed to 'build' on the achieved CRs, should therefore be evaluated in these patients.

High-dose treatment and relevant prognostic factors

University of Arkansas experience with tandem transplants

Application of melphalan-based tandem autotransplants, with a curative intent, was first tested by the University of Arkansas group (Total Therapy 1 (TT1)) in 231 newly diagnosed or minimally pretreated patients; one and two courses of HDT were given to 84 and 71%, respectively.²¹ An increment in (stringently defined) CR rate, from 26% after one to 38% after two transplants on an intent-to-treat analysis, was seen (32 and 48% for patients who actually completed the intended treatment). The median EFS and OS were 30 and 68 months, respectively. Superior prognosis was seen in the absence of unfavorable karyotypes (chromosomes 13(Δ 13) and 11q abnormalities) and high β -2 microglobulin (β -2m) levels. Time-dependent covariate analysis suggested that timely application of the second transplant (<6 months from the first one) did significantly extend both EFS and OS, independent of cytogenetics and β -2m levels.

Two additional cytogenetic parameters strongly associated with poor prognosis in MM are the presence of hypodiploidy and the so-called MM-MDS karyotype. It has recently been postulated that the poor prognosis of Δ 13 is entirely due to its frequent association with hypodiploidy, which is the real poor prognostic factor.²² Analyzing our experience in 1475 MM patients intended to be treated with melphalan-based HDT and ASCT, we showed that both hypodiploidy and Δ 13 (65% overlap rate with hypodiploidy) independently impart a poor prognosis in MM patients. The incorporation of pre-transplant- β -2m >2.5 mg/l and albumin \leq 35 g/l in the prognostic model did not appreciably alter the EFS and OS as predicted by the classification

based only on cytogenetics.²³ The OS and EFS curves of the subgroup of 148 previously untreated TT1 patients based on the presence of Δ 13 and/or hypodiploidy are depicted in Figure 1.

The presence of MDS-like cytogenetic abnormalities [del 5q, del 7q, add 8, del 20q, t(1;7)] in an otherwise typical for MM karyotype (MM-MDS) was recently found to impart a poor prognosis even after adjusting for any and all individual cytogenetic abnormalities.²⁴ Further investigation is needed in order to clarify the underlying biologic significance of this finding. The OS curve of over 2000 patients according to the detection of MM-MDS vs other karyotypes is depicted in Figure 2.

The significance of elevated serum lactate dehydrogenase (LDH) levels in predicting poor prognosis has long been recognized in non-Hodgkin's lymphoma, but also in MM.²⁵ Elevated serum LDH at diagnosis has emerged as a significant prognostic factor in our analysis of 148 previously untreated TT1 patients who received at least one autotransplant. The combined use of Δ 13-hypodiploidy/LDH levels identified subgroups with distinct prognosis. The median OS for patients with no Δ 13-hypodiploidy/normal (<190 U/l) LDH was 8.2 years (vs 4.3 and 3.1 years for the groups with high LDH (irrespective of cytogenetic

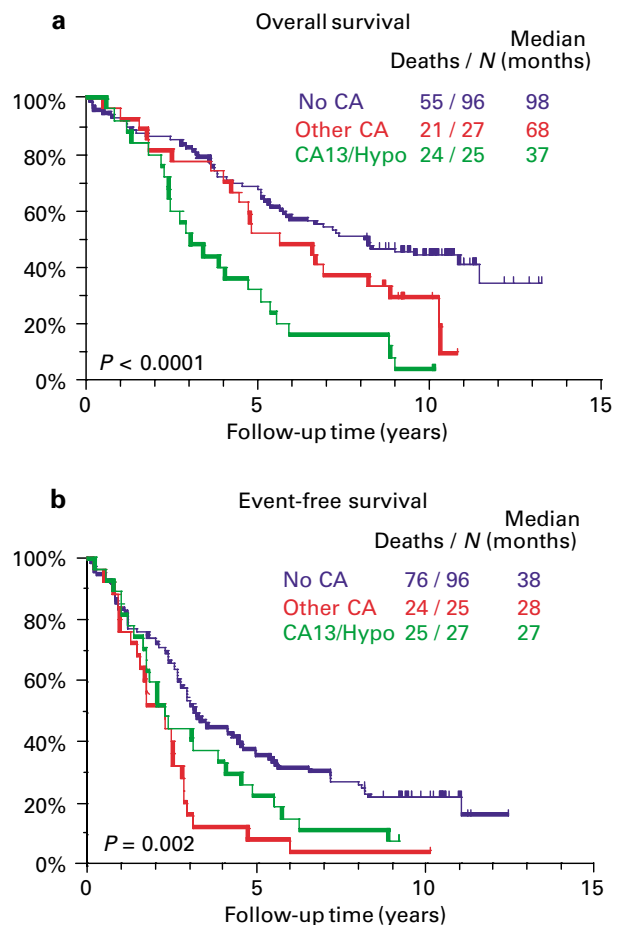


Figure 1 OS (panel a) and EFS (panel b) of 148 previously untreated TT1 patients according to absence of cytogenetic abnormalities (no CA); abnormalities involving chromosome 13 deletion or hypodiploidy (CA 13, hypodiploidy); or other CA.

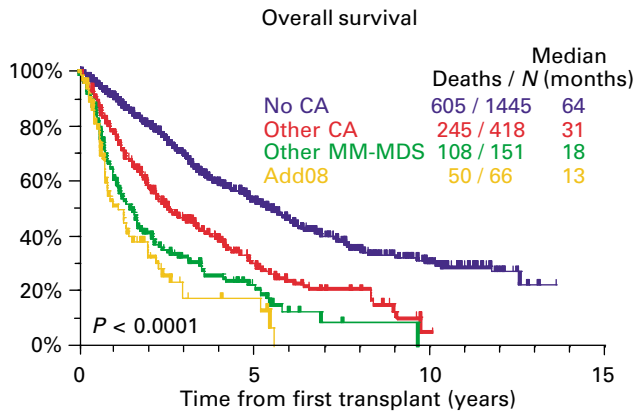


Figure 2 MDS-like signature as part of MM karyotype abnormalities (MM-MDS) on survival among 2080 patients enrolled in melphalan-based tandem transplant trials.

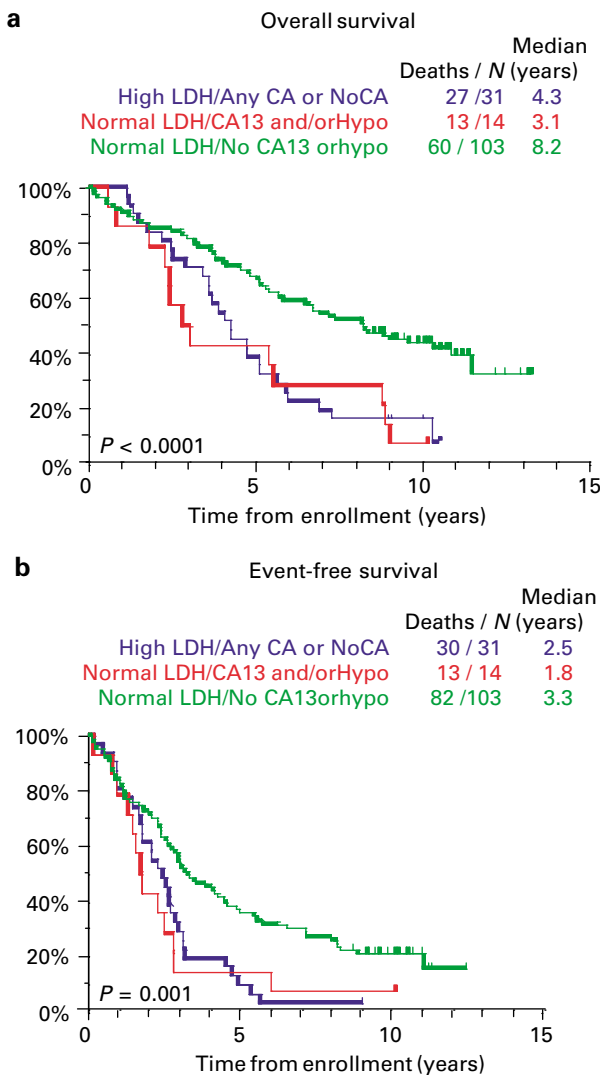


Figure 3 OS (panel a) and EFS (panel b) based on CA13/hypodiploidy and serum LDH levels in 146 previously untreated TT1 patients.

abnormalities) and with $\Delta 13$ and/or hypodiploidy/normal LDH, respectively) (Figure 3).

With a median follow-up of 9 years, the prognostic implications of individual cytogenetic abnormalities in TT1 patients, were examined both at baseline and at follow-up bone marrow (BM) examination.²⁶ Superior prognosis was associated with the absence of any cytogenetic abnormalities at both diagnosis and relapse (10-year OS: 40%). On multivariate analysis, hypodiploidy/ $\Delta 13$ (present in 16% of patients at baseline) was the most important unfavorable cytogenetic parameter, independently associated with both short EFS and OS. Elevated LDH retained its independent unfavorable prognostic impact for OS.

Intensifying high-dose treatment-total therapy II

Intensification of TT1 is currently employed in total therapy II (TT2) trial (also randomizing patients to upfront thalidomide). Besides the addition of thalidomide, this protocol was designed to deliver more intensive treatment by intensifying remission induction treatment, adding consolidation chemotherapy during the first post-transplant year and providing pulse dexamethasone during the first year of interferon administration (second post-transplant year). Comparison of the outcome of the first 144 TT2 patients with at least 4 years of follow-up vs the 231 TT1 patients (median follow-up: 10 years) revealed significantly higher CR and near CR rates as well as superior EFS in the patients treated in the TT2 trial (Figure 4). The higher CR incidence was observed especially in the patients without baseline cytogenetic abnormalities. When patients achieving at least near CR were compared, 2-year estimates of near CR were superior in TT2 vs TT1 (true even for patients with hypodiploidy/ $\Delta 13$). CR duration (as surrogate marker for cure) was prolonged in TT2 vs TT1 and was adversely affected by the presence of cytogenetic abnormalities and elevated LDH levels (Figure 5). This evidence confirms that survival can be prolonged through treatment intensification and CR achievement. The relapse risk for TT1 and TT2 patients overall and according to cytogenetic abnormalities is depicted in Figure 6.

Tandem transplants-randomized trials

The concept of tandem transplants has been tested in a randomized fashion by several European groups. The IFM 94 trial tested one (melphalan/total body irradiation (TBI)) vs two (melphalan followed by melphalan/TBI) transplants; with a median follow-up of 6 years, the median EFS and OS were superior in the double vs the single transplant arm (30 and 58 months vs 25 and 48 months, respectively; $P = 0.03$ and 0.01 , respectively).¹⁹ The EFS and OS curves separated only after 3 years of follow-up. Younger age, low serum LDH and β -2m levels and tandem transplants were associated with longer OS on multivariable analysis. Patients who achieved less than near CR after the first transplant appeared to have the biggest benefit from two transplants. The importance of achieving post-transplant CR was also supported by a recent phase II trial conducted by the Spanish GELTAMO group.²⁷

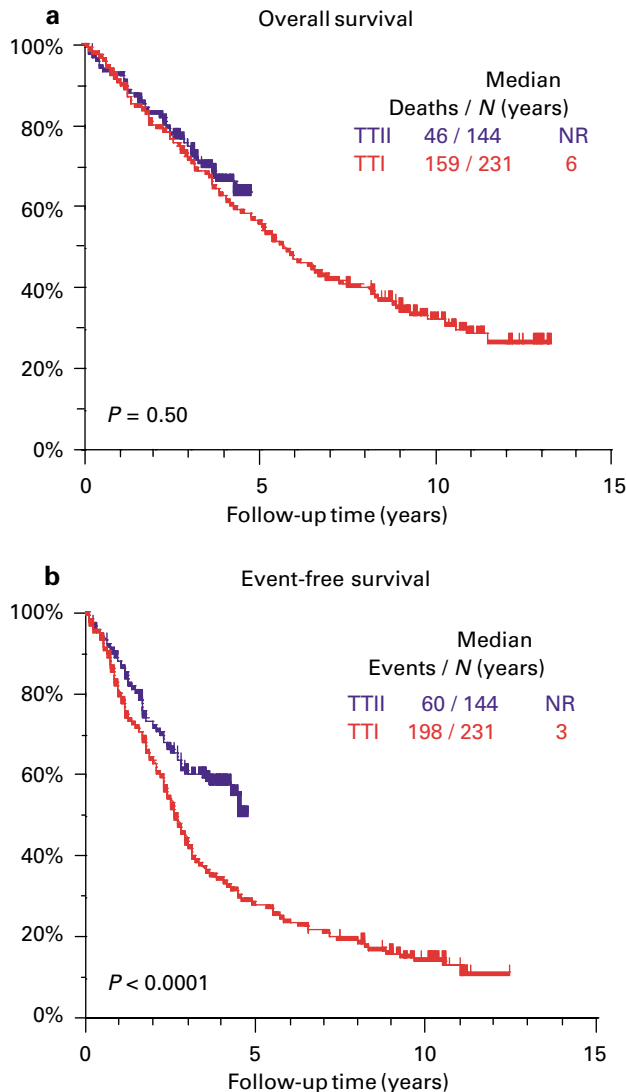


Figure 4 Superior EFS (panel b) in 144 TT2 patients with at least 4-year follow-up vs 231 TTI patients; no statistically significant difference is yet seen in OS (panel a0) (NR: not reached).

The French study (MAG 95) tested one (melphalan/etoposide/cyclophosphamide/TBI) transplant vs two (melphalan followed by melphalan/etoposide/cyclophosphamide/TBI) transplants; with a median follow-up of 53 months, there was no difference in CR rate, EFS and OS.²⁸ The Italian study (BOLOGNA 96) tested one (melphalan) transplant vs two (melphalan followed by melphalan/busulfan) transplants; no difference in CR rates was seen.²⁹ A statistically significant superior EFS for the two transplants arm has already been detected. With a median follow-up of 38 months, no difference in OS was yet observed. The Dutch-Belgian HOVON study (fully reported) compared intermediate-dose melphalan (70 mg/m² × 2) without stem-cell support with the same regimen followed by one transplant (TBI, cyclophosphamide); with a median follow-up of 33 months, higher CR rate and longer time to progression were detected in the transplant arm. However, OS was not different (50 vs 47 months) in the two arms.³⁰ All studies have a rather limited follow-up.

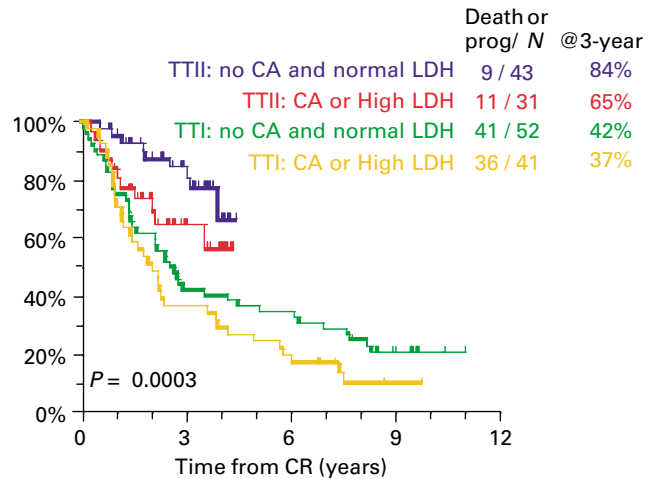


Figure 5 Impact of cytogenetic abnormalities and serum LDH levels on CR duration on TT1 and TT2.

It is worth remembering that in the IFM 94 trial the separation in the EFS and OS curves only occurred after 3 years of follow-up (with the interim analysis revealing no difference between the arms). Furthermore, it is now known that TBI-based regimens are inferior to melphalan alone.^{31,32} Finally, salvage transplants offered at relapse may well obscure the OS benefit of tandem transplants. A summary of these trials comparing one vs two courses of high-dose chemotherapy with autologous stem cell support is shown in Table 1.

New agents

Thalidomide

The introduction of thalidomide in the clinical arena was prompted by the observation that increased neovascularization does occur in BM biopsies from myeloma patients and is prognostically relevant.³³ Thalidomide was, at the time (1998), the only drug available with major antiangiogenic activity. It is now known that thalidomide exerts a plethora of effects targeting the interaction between malignant plasma cells and BM microenvironment as well as various aspects of the immune system.³⁴ Despite lack of correlation between response rate and microvessel density in the BM biopsies, our landmark study reported an overall response rate ($\geq 50\%$ reduction in monoclonal component) of 32% – with a median time to response of 1 month – in a group of 84 relapsing patients following at least one course of HDT.⁸ The median response duration was approximately 15 months. In an update of 169 MM patients, absence of cytogenetic abnormalities, low β -2 m levels and low plasma cell labeling index (PCLI) as well as higher cumulative thalidomide dose were associated with superior survival.³⁵ These results have been reproduced by several investigators. Advanced age, high LDH levels and impaired renal function predicted for poor EFS and OS in a phase II multicenter trial,³⁶ while higher cumulative thalidomide dose during the first 3 months of treatment was associated with improved survival.^{37,38}

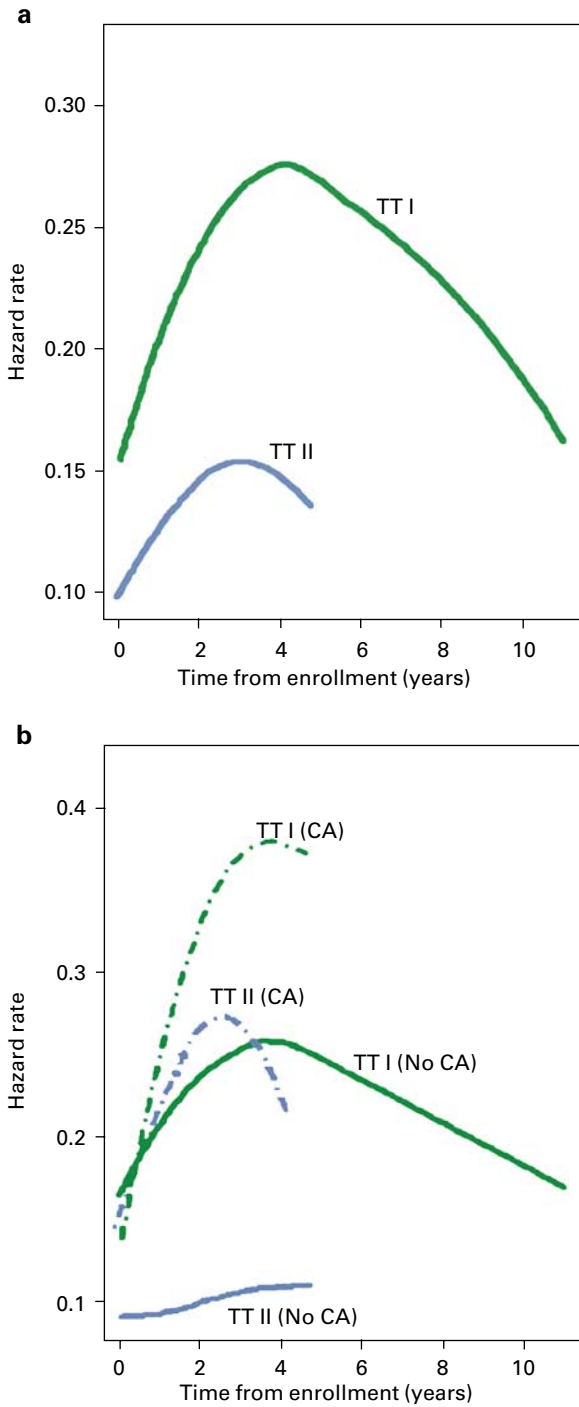


Figure 6 Relapse risk for TT1 and TT2 patients overall (panel a) and based on the presence of cytogenetic abnormalities (panel b).

Proteasome inhibitors ± thalidomide

Proteasome inhibitors represent another novel approach of targeting MM cells and their microenvironment. In a phase II trial of 202 heavily pretreated (64% of them had failed HDT and 83% thalidomide) patients, bortezomib induced a response rate of 35% (including some CRs) with an acceptable toxicity profile.⁹ On multivariate analysis,

response rates were lower in patients with abnormal BM cytogenetic analysis (but not deletion of chromosome 13) and $\geq 50\%$ BM infiltration by plasma cells.³⁹ At our institution, the combination of bortezomib/thalidomide ± dexamethasone has yielded a response rate ($> 50\%$ reduction in monoclonal component) of 57% when tried in 56 heavily pretreated patients.⁴⁰ No aggravation (although the follow-up is limited) of pre-existing thalidomide-induced neurotoxicity by bortezomib or any synergistic toxicity between the two agents were detected. EFS and OS were superior in patients presenting without cytogenetic abnormalities at relapse. The EFS and OS curves updated (by 02/04) for the first 70 patients in the study, according to the presence of cytogenetic abnormalities, are shown in Figure 7.

Revimid

The drug, a small-molecule thalidomide derivative, lacks the sedative and neurotoxic side effects of the parent compound. Revimid was administered at escalating doses (5, 10, 25 and 50 mg/day) to 27 MM patients with refractory/relapsing disease, mostly after HDT and thalidomide. The maximum tolerated dose was considered to be 25 mg/day, with significant myelosuppression seen at the higher dose level of 50 mg/day. Seven (26%) patients had at least 50% reduction in monoclonal component.⁴¹ We confirmed these results in a group of 52 heavily pretreated patients by using the same cumulative dose of revimid administered in two different schedules (25 mg × 20 doses and 50 mg × 10 doses every 28 days).⁴² We observed higher response rates with the more prolonged 25 mg dose schedule (Figure 8). Greater than grade II, thrombocytopenia was linked to lower pretreatment platelet counts as a reflection of limited hematopoietic reserve.

Low-risk patients

The mere prolongation of EFS and OS as an effect of a therapeutic modality (as has been convincingly shown in several trials of HDT and ASCT) is, by no means, equivalent to cure. Instead, a plateau has to be shown in the survival curves. In a recent update of the TT1 protocol, we focused on 146 (of 231 enrolled) patients who received tandem autotransplants ≤ 12 months apart (131 had their transplants < 6 months apart) and survived ≥ 2 months after the second transplant.⁴³ With a median follow-up of 9.3 years after enrollment, 31 (21%) patients remain in either complete or stable partial remission, requiring no additional intervention than the maintenance treatment outlined in the protocol. A total of 31 additional patients are alive on different treatments for relapsing disease. In seven of these 31 patients, the interval between relapse and date of analysis is already longer than the interval between the first transplant and relapse. When prognostic factors were analyzed in the subgroup of relapsed patients, only the detection of cytogenetic abnormalities and $\beta\text{-2m} > 4 \text{ mg/l}$ (both at relapse) retained their significance for postrelapse survival. The EFS and OS curves of over 2000 patients, with prolonged follow-up, according to cytogenetic

Table 1 Summary of single vs tandem transplant trials in MM

Author	Regimens	N	Median Age (years)	Median FU (months)	% CR (P)	Median EFS (months) (P)	Median OS (months) (P)
Attal (IFM 94)	VAD × 3-4 → G-CSF → MEL 140 + TBI 8 Gy vs VAD × 3-4 → G-CSF → MEL 140; MEL 140 + TBI 8 Gy	199 vs 200	52 vs 52	75	42 vs 50 ≥ nCR (<0.1)	25 vs 30 (<0.03)	48 vs 58 (0.01)
Cavo (BOLOGNA 96)	VAD × 4 → CTX → MEL 200 vs VAD × 4 → CTX → MEL 200; MEL 120 + busulfan	110 vs 110	53 vs 53	38	21 vs 24 NS	25 vs 34 (<0.05)	56 vs 60 NS
Fermand (MAG 95)	DEX × 2 → CTX → VAD × 3-4 → MEL 140 + VP16 + CTX + TBI 12 Gy vs DEX × 2 → CTX → × 3-4 → MEL 140; MEL 140 + VP16 + TBI 12 Gy	97 vs 96	50 vs 50	53	39 vs 37 NS	31 vs 33 NS	49 vs 73 NS
Segeren (HOVON)	VAD × 3-4 → CTX → MEL 70 × 2 vs VAD × 3-4 → CTX → MEL 70 × 2 → CTX + TBI 9 Gy	129 vs 132	55 vs 56	33	13 vs 29 (0.002)	21 vs 22 NS	50 vs 47 NS

nCR: near Complete Remission.

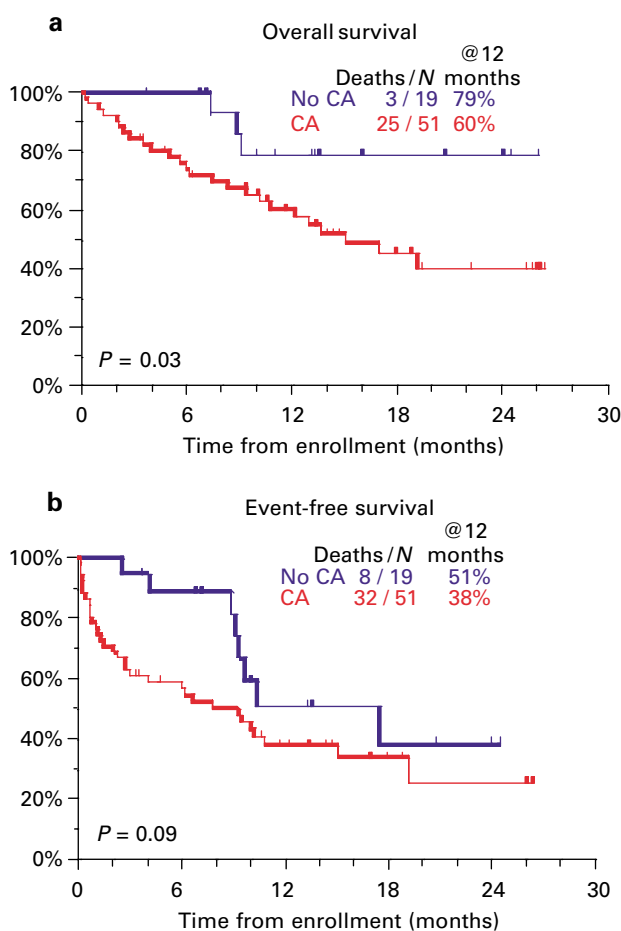


Figure 7 OS (panel a) and EFS (panel b) of 70 patients treated with bortezomib + thalidomide based on the presence of cytogenetic abnormalities.

abnormalities are depicted in Figure 9; a plateau consistent with cure is apparent in patients without cytogenetic abnormalities.

These data suggest that cure is possible in a subset of MM patients. These patients either have achieved (and maintain) CR or continue to have partial remission with

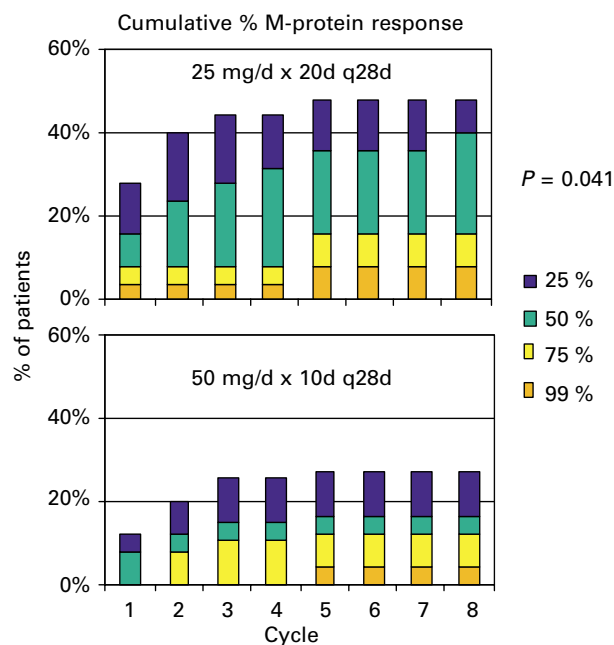


Figure 8 Revimid for advanced/refractory myeloma: response kinetics according to dosing schedule.

small (stable) levels of monoclonal protein and minimal marrow plasmacytosis (likely regression to an MGUS phase). For all practical purposes, they can be compared to patients with good-risk diffuse large-cell lymphoma who are cured from their disease achieving either complete radiologic remission or remaining with stable, residual, non-viable lymphadenopathy (complete remission unconfirmed). Another subgroup of MM patients can enjoy long survival interrupted, however, by relapses. As long as there is no detection of cytogenetic abnormalities, application of various therapeutic modalities (thalidomide, further cytotoxic chemotherapy including HDT, bortezomib, etc) will very likely reinduce long-lasting remissions. These patients can be compared to patients with follicular lymphoma, the prototypic hematologic malignancy characterized by remissions and relapses, in which recently introduced treatments

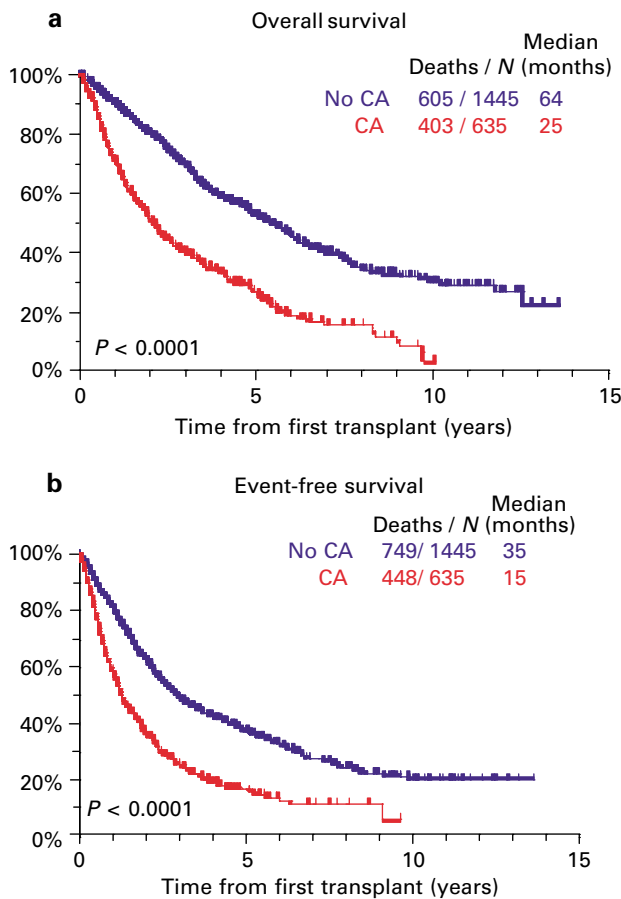


Figure 9 OS (panel a) and EFS (panel b) of 2080 patients based on the presence of baseline cytogenetic abnormalities; plateau in the survival curves is consistent with cure.

(radioconjugated monoclonal antibodies)⁴⁴ may change the natural history of the disease by inducing longer remissions than the ones achieved with previous lines of treatment. Unfortunately, as in follicular lymphoma, patients with this form of ‘chronic remitting and relapsing myeloma’ are obviously at risk for ‘transformation’; the acquisition of new cytogenetic abnormalities will lead to the development of *genetic resistance* (which, in contrast to *epigenetic resistance* cannot be overcome by HDT) by the malignant clone, which will now be characterized by complete independence of the bone marrow stroma, higher proliferative potential and frequent extramedullary manifestations. This is exactly the group of patients in whom, at least on theoretical grounds, a survival benefit may be anticipated through achieving higher CR rate (incorporation of thalidomide as in TT2 trial or other agents) and decreasing the chances of ‘transformation’ to a more biologically aggressive disease variant.

High-risk patients

For high-risk patients (comprising approximately 30% of the total), that is, patients with any chromosome 13 abnormalities, hypodiploidy (overlapping with chromo-

some 13 abnormalities in 65% of patients) and the so-called MM-MDS karyotype, and/or elevated baseline LDH levels, even the timely application of tandem transplants is not a curative approach. They can be compared to poor-risk diffuse large-cell lymphoma patients. The less pronounced benefit in such patients may be due to the malignant clone’s inherent *genetic resistance* with resultant less cytoreduction beyond the clinical CR detection threshold. Sensitive methods to monitor minimal residual disease levels will clarify this issue. Faster regrowth kinetics between the chemotherapy courses may also contribute to the poor prognosis in this patient group; the observed pattern of early relapse even during the remission induction treatment phase supports this notion. Alternatively, epigenetic factors derived from an activated BM microenvironment may feed the growth of myeloma cells and induce drug resistance. Our ongoing research focuses on addressing these issues both at laboratory and clinical levels. Currently allogeneic transplant is a potentially curative approach in this high-risk group.

Allogeneic transplant

Allogeneic transplantation with its well-established immunologically mediated graft-versus-myeloma⁴⁵ effect is an attractive option in, otherwise suitable for the procedure, high-risk patients. The conventional, fully myeloablative, allotransplant is applicable in a small minority of affected patients and has been associated with considerable (30–50%) TRM and other toxicities.^{46,47} The recent advent of the so-called ‘mini-transplants’ (nonmyeloablative transplants) with their decreased immediate post-transplant toxicity has allowed the more ‘liberal’ use of the procedure by expanding the pool of the potential recipients.

The Seattle group, in an effort to decrease TRM, separated the immunotherapeutic effect of the allogeneic transplant from the toxicity of the HDT; the cytoreduction induced by autotransplant (with low TRM) was combined with the curative potential of a subsequent ‘mini-transplant’.⁴⁸ A total of 54 previously treated MM patients (median age: 52 years, 52% refractory/relapsed disease) received melphalan 200 mg/m² and ASCT followed (in 52 patients) 40–229 days later (median: 62), by TBI (200 cGy), immune suppression with mycophenolate mofetil (for 1 month) and cyclosporine (for at least 2 months) and unmanipulated peripheral blood stem cells from HLA-matched siblings. All (52) engrafted post-allotransplant; the 100-day TRM was 0%. With a median follow-up of about 18 months after the allograft, the OS is 78%. In total, 12 patients have died (11 after allograft, mainly due to progressive disease and GvHD-related complications). Acute graft-versus-host disease (GvHD) developed in 38% of the patients (mostly grade II), while 46% required treatment for chronic GvHD. The overall response rate was 83% (CR of 57%). Longer follow-up will be needed before the curative potential of this promising approach can be fully appreciated.

Recently, others have reported similar results with the application of dose-reduced conditioning regimen (melphalan, fludarabine, antithymocyte globulin) and allogeneic transplant from either a related or unrelated donor

Table 2 Autologous followed by allogeneic transplant trials in MM

Author	Regimens	N	Median age (years)	Median FU (months)	% CR	Estimated 2-year OS (%)	Estimated 2-year EFS (%)
Maloney	MEL 200 → TBI 2 Gy	54	52	18	57	78	55
Kröger	MEL 200 → Fludara/MEL 100/ATG	17	51	13	73	74	56

following an autologous transplant (Mel 200 mg/m²).⁴⁹ The median interval between the two transplants was 4 months. Strictly defined CR rate was 73% after allografting. Of 17 patients with advanced myeloma, 13 are alive (12 progression-free) with a median follow-up of 13 months after the allogeneic transplant. A summary of these trials consisting of autologous followed by 'by design' allogeneic transplant is shown in Table 2.

The preliminary results of two IFM protocols (IFM9903 and IFM 9904) have been recently presented in an abstract form.⁵⁰ Patients with high-risk features (serum β -2m > 3 mg/l and chromosome 13 deletion by FISH) received a brief remission induction treatment (VADX4) followed either by two courses of ASCT (Mel 200 mg/m², Mel 220 mg/m² ± anti-IL6 monoclonal antibody) (IFM 9904) or one course of ASCT (Mel 200 mg/m²) followed by 'mini-transplant' (fludarabine, antithymocyte globulin and low-dose busulfan) from an available HLA-matched sibling (IFM 9903). 'Mini-transplant' was actually given to 29/45 (64%) and two courses of ASCT were actually given to 73/105 (69%) of the patients enrolled. With a limited follow-up, the median EFS is 21 months in the 9903 and 25 months in the 9904 trial ($P=0.08$); the 3-year survival from diagnosis is 52% and 54% respectively ($P=0.37$).

In a similar fashion, we performed allogeneic 'mini-transplants', from HLA-matched siblings (mainly) or unrelated donors, in 31 high-risk patients (median age: 56 years) using melphalan 100 mg/m² and cyclosporine for GvHD prophylaxis.⁵¹ We reported superior outcome when the 'mini-transplant' was performed at chemosensitive relapse and after 1 vs >1 prior ASCT. Indeed, chemosensitive disease and adequate performance status were the only significant factors for EFS and OS in our recent analysis of 45 such patients.⁵² We currently recommend (nonmyeloablative) allotransplant (preferably from HLA-matched sibling) after one ASCT, only in high-risk patients based on baseline cytogenetic evaluation and elevated LDH levels.

Based on the encouraging preliminary data reported by the Seattle group, a trial launched by Bone Marrow Transplant-Clinical Trials Network (BMT-CTN) will compare tandem autotransplants (with or without post-transplant maintenance) vs one autologous followed by allogeneic, nonmyeloablative transplant in patients with an available HLA-matched sibling. Although the trial will likely provide information regarding the benefit of post-transplant maintenance, no consideration has been given to the disease risk stratification. The TRM of 'mini-transplants' performed in a multicenter setting is not expected to be <20% and there is considerable morbidity due to GvHD; although the risk may be well justified in patients

with high-risk cytogenetic abnormalities, such a risk is unacceptable in low-risk patients.

Conclusions – future directions

We propose that application of a comprehensive treatment approach, based on tandem autotransplants, in newly diagnosed myeloma patients will cure a substantial minority (approximately 10–15%) of them. This subgroup, characterized by low β -2m and LDH levels and the absence of adverse cytogenetic abnormalities, comprises patients with true CR and patients with persistently detectable, stable monoclonal protein. An additional 20–25% of patients (with the same favorable baseline features) will enjoy a long survival, interrupted, however, by responsive relapses. These patients remain at risk for 'transformation' to aggressive myeloma. Our early experience with the intensified chemotherapy, as delivered in TT2 trial, at least suggests that true, stringently defined, CR is critical in increasing the cure rate in this patient subgroup. The benefit of any post-transplant manipulations, although widely used in our institution, remains to be proven for these groups of patients.

The remaining patients, characterized by adverse cytogenetic abnormalities and high LDH levels, will derive a less meaningful survival benefit from HDT and ASCT as currently employed. Upfront use of novel agents (bortezomib, revimid) targeting not only the malignant cells but the stromal elements (which by paracrine action 'feed' the growth and survival of tumor) as well, in combination with intensive HDT may increase the proportion of patients achieving cure or long-term disease control in this high-risk group. Currently, allogeneic transplant appears to be a potentially curative approach for these patients; further understanding of the GvHD and the graft-versus-myeloma effect mechanisms will likely render the procedure more effective.

The optimal integration of new drugs in clinical practice will be achieved at a much faster pace (and definitely in a more rational way) by using the gene expression profiling (GEP) technology.⁵³ This approach is expected to allow in the near future more 'clever' selection of novel agents in treating individual patients, better understanding of a specific drugs' mechanism of action and development of agents specific for (so far) unrecognized targets. Responding to these challenges should be viewed as an exciting opportunity (by clinicians and basic researchers alike) towards increasing the proportion of patients being cured from a disease for which palliation was considered a reasonable achievement even up to 10 years ago.

Acknowledgements

This work was supported in part by CA55819 from the National Cancer Institute, Bethesda, MD, USA.

References

- 1 Samson D. Principles of chemotherapy and radiotherapy. In: Gahrton G, Durie BGM (eds.). *Multiple Myeloma*. Arnold: London, 1996; pp 108–129.
- 2 Myeloma Trialists' Collaborative Group. Combination chemotherapy vs melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *J Clin Oncol* 1998; **16**: 3832–3842.
- 3 Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 1984; **310**: 1353–1356.
- 4 Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. *Am J Hematol* 1990; **33**: 86–89.
- 5 McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. *Lancet* 1983; **2**: 822–824.
- 6 Vesole DH, Tricot G, Jagannath S et al. Autotransplants in multiple myeloma: what have we learned? *Blood* 1996; **88**: 838–847.
- 7 Raje N, Powles R, Kulkarni S et al. A comparison of vincristine and doxorubicin infusional chemotherapy with methylprednisolone (VAMP) with the addition of weekly cyclophosphamide (C-VAMP) as induction treatment followed by autografting in previously untreated myeloma. *Br J Haematol* 1997; **97**: 153–160.
- 8 Singhal S, Mehta J, Desikan R et al. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; **341**: 1565–1571.
- 9 Richardson P, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003; **348**: 2609–2617.
- 10 Berenson JR, Lichtenstein A, Porter L et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med* 1996; **334**: 488–493.
- 11 Berenson JR, Lichtenstein A, Porter L et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 1998; **16**: 593–602.
- 12 Osterborg A, Brandberg Y, Molostova V et al. Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin Beta, in hematologic malignancies. *J Clin Oncol* 2002; **20**: 2486–2494.
- 13 Dudeney S, Lieberman IH, Reinhardt MK et al. Kyphoplasty in the treatment of osteolytic vertebral compression fractures as a result of multiple myeloma. *J Clin Oncol* 2002; **20**: 2382–2387.
- 14 Cotten A, Dewatre F, Cortet B et al. Percutaneous vertebroplasty for osteolytic metastases and myeloma: effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up. *Radiology* 1996; **200**: 525–530.
- 15 Barlogie B, Jagannath S, Vesole D et al. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997; **89**: 789–793.
- 16 Lenhoff S, Hjorth M, Holmberg E et al. Impact on survival of high doses therapy with autologous stem cell supporting patients younger than 60 years with newly diagnosed multiple myeloma: a population based study. *Blood* 2000; **95**: 7–11.
- 17 Attal M, Harousseau JL, Stoppa AM et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 1996; **335**: 91–97.
- 18 Child JA, Morgan GI, Davies FE et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003; **348**: 1875–1883.
- 19 Attal M, Harousseau JL, Facon T et al. Single vs double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003; **349**: 2495–2502.
- 20 Miyamoto T, Nagafuji K, Akashi K et al. Persistence of multipotent progenitors expressing AML1/ETO transcripts in long-term remission patients with t(8;21) acute myelogenous leukemia. *Blood* 1996; **87**: 4789–4796.
- 21 Barlogie B, Jagannath S, Desikan KR et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. *Blood* 1999; **93**: 55–65.
- 22 Smadja N-V, Bastard C, Brigaudeau C et al. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood* 2001; **98**: 2229–2238.
- 23 Fassas AB-T, Spencer T, Sawyer J et al. Both hypodiploidy and deletion of chromosome 13 independently confer poor prognosis in multiple myeloma. *Br J Haematol* 2002; **118**: 1041–1047.
- 24 Jacobson J, Barlogie B, Shaughnessy J et al. MDS-type abnormalities with myeloma signature karyotype (MM-MDS). *Br J Haematol* 2003; **122**: 430–440.
- 25 Barlogie B, Smallwood L, Smith T, Alexanian R. High serum levels of lactic dehydrogenase identify a high-grade lymphoma-like myeloma. *Ann Intern Med* 1989; **110**: 521–525.
- 26 Shaughnessy J, Jacobson J, Sawyer J et al. Continuous absence of metaphase-defined cytogenetic abnormalities, especially of chromosome 13 and hypodiploidy, ensures long-term survival in multiple myeloma treated with total therapy I: interpretation in the context of global gene expression. *Blood* 2003; **101**: 3849–3856.
- 27 Lahuerta JJ, Grande C, Martinez-Lopez J et al. Tandem transplants with different high-dose regimens improve the complete remission rates in multiple myeloma. *Br J Haematol* 2003; **120**: 296–303.
- 28 Femand JP, Marolleau JP, Alberti C. Single vs tandem high-dose therapy (HDT) supported with autologous blood stem cell (ABSC) transplantation using unselected or CD-34 enriched ABSC: preliminary results of a two by two design randomized trial in 230 young patients with multiple myeloma. *Blood* 2001; **98**: 815a (abstract 3387).
- 29 Cavo M, Tosi P, Zagnagni E et al. The Bologna 96 clinical trial of single vs double PBSC transplantation for previously untreated MM: results of an interim analysis. *Blood* 2002; **100**: 17a (abstract 669).
- 30 Segeren CM, Sonneveld P, van der Holt B et al. Overall and event free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study. *Blood* 2003; **101**: 2144–2151.
- 31 Moreau P, Facon T, Attal M et al. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood* 2002; **99**: 731–735.
- 32 Desikan KR, Tricot G, Dhodapkar M et al. Melphalan plus total body irradiation (MEL-TBI) or cyclophosphamide

- (MEL-CY) as a conditioning regimen with second autotransplant in responding patients with myeloma is inferior compared to historical controls receiving tandem transplants with melphalan alone. *Bone Marrow Transplant* 2000; **25**: 483–487.
- 33 Vacca A, Ribatti D, Roncali L *et al*. Bone marrow angiogenesis and progression in multiple myeloma. *Br J Haematol* 1994; **87**: 503–508.
- 34 Anderson K. Moving disease biology from the laboratory to the clinic. *Semin Oncol* 2002; **29** (Suppl. 17): 17–20.
- 35 Barlogie B, Zangari M, Spencer T *et al*. Thalidomide in the management of multiple myeloma. *Semin Hematol* 2001; **38**: 250–259.
- 36 Mileskkin L, Biagi JJ, Mitchell P *et al*. Multicenter phase 2 trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. *Blood* 2003; **102**: 69–77.
- 37 Neben K, Moehler T, Benner A *et al*. Dose-dependent effect of thalidomide on overall survival in relapsed multiple myeloma. *Clin Cancer Res* 2002; **8**: 3377–3382.
- 38 Yakoub-Agha I, Attal M, Dumontet C *et al*. Thalidomide in patients with advanced multiple myeloma: a study of 83 patients – report of the Intergroupe Francophone du Myelome (IFM). *Hematol J* 2002; **3**: 185–192.
- 39 Richardson PGG, Barlogie B, Berenson J *et al*. Prognostic factors associated with response in patients with relapsed and refractory multiple myeloma (MM) treated with bortezomib. *ASCO Meeting Proceedings* 2003; **102** (Abstract 581).
- 40 Zangari M, Barlogie B, Jacobson J *et al*. VTD regimen comprising velcade (V) + Thalidomide (T) and added DEX (D) for non-responders to V+ effects a 57% PR rate among 56 patients with myeloma (M) relapsing after autologous transplant. *Blood* 2003; **102**: 236a (abstract 830).
- 41 Richardson PG, Schlossman R, Weller E *et al*. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 2002; **100**: 3063–3067.
- 42 Zangari M, Barlogie B, Jacobson J *et al*. Revimid 25 mg (REV 25) × 20 *vs* 50 mg (REV 50) × 10 q 28 days with bridging of 5 mg × 10 *vs* 10 mg × 5 as post-transplant salvage therapy for multiple myeloma (MM). *Blood* 2003; **102**: 450a (abstract 1642).
- 43 Fassas AB, Barlogie B, Ward S *et al*. Survival after relapse following tandem autotransplants in multiple myeloma patients: the University of Arkansas total therapy I experience. *Br J Haematol* 2003; **123**: 484–489.
- 44 Kaminski M, Zelenetz A, Press O *et al*. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol* 2001; **19**: 3908–3911.
- 45 Tricot G, Vesole DH, Jagannath S *et al*. Graft-versus-myeloma effect: proof of principle. *Blood* 1996; **87**: 1196–1198.
- 46 Bensinger WI, Buckner CD, Anasetti C *et al*. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood* 1996; **88**: 2787–2793.
- 47 Bjorkstrand BB, Ljungman P, Svensson H *et al*. Allogeneic bone marrow transplantation *vs* autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood* 1996; **88**: 4711–4718.
- 48 Maloney DG, Molina AJ, Sahebi F *et al*. Allografting with non-myeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood* 2003; **102**: 3447–3545.
- 49 Kröger N, Schwerdtfeger R, Kiehl M *et al*. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood* 2002; **100**: 755–760.
- 50 Moreau P, Garban F, Falcon T *et al*. Preliminary results of the IFM9903 and IFM9904 protocols comparing autologous followed by miniallogeneic transplantation and double autologous transplant in high-risk *de novo* multiple myeloma. *Blood* 2003; **102**: 43a (#138).
- 51 Badros A, Barlogie B, Morris C *et al*. High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. *Blood* 2001; **97**: 2547–2549.
- 52 Lee CK, Badros A, Barlogie B *et al*. Prognostic factors in allogeneic transplantation for patients with high-risk multiple myeloma after reduced intensity conditioning. *Exp Hematol* 2003; **31**: 73–80.
- 53 Zhan F, Hardin J, Kordsmeier B *et al*. Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. *Blood* 2002; **99**: 1745–1757.