Advances in Therapy of Multiple Myeloma: Lessons from Acute Leukemia

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Abstract
This paper traces the lack of progress, until recently, in the treatment of multiple myeloma (MM) to having ignored the principles that led to cure in acute leukemia more than 2 decades ago. Only in the mid-1980s did investigation begin to consider complete remission (CR) a research objective, representing a necessary first step toward cure. The experience with autologous and allogeneic stem cell-supported high-dose therapy is reviewed, demonstrating, in both historically controlled and randomized studies, the validity of the dose-response concept in MM in terms of increased CR rates as well as extended event-free (EFS) and overall survival (OS). Avoidance of hematopoietic stem cell-damaging agents, especially melphalan, nitrosoureas, and ionizing radiation to marrow-containing sites, assures the ability of peripheral stem cell collection of high quality and quantity, providing rapid engraftment so that mortality is well under 5% following high-dose melphalan (200 mg/m²). This treatment can be applied safely to patients even >70 years of age and in the presence of renal failure. Tandem autotransplants after multiregimen induction have yielded CR rates in the 40% range with median durations of EFS and OS of 43 and 62 months, respectively. Certain chromosomal abnormalities (11 and 13; and translocations) represent the dominant risk of intervention (11-13) and, increasingly in recent years, molecular abnormalities (12). Thus, distinct entities of leukemia are now reserved for the treatment of multiple myeloma (MM) to having ignored the principles that led to cure in acute leukemia more than 2 decades ago. Only in the mid-1980s did investigation begin to consider complete remission (CR) a research objective, representing a necessary first step toward cure. The experience with autologous and allogeneic stem cell-supported high-dose therapy is reviewed, demonstrating, in both historically controlled and randomized studies, the validity of the dose-response concept in MM in terms of increased CR rates as well as extended event-free (EFS) and overall survival (OS). Avoidance of hematopoietic stem cell-damaging agents, especially melphalan, nitrosoureas, and ionizing radiation to marrow-containing sites, assures the ability of peripheral stem cell collection of high quality and quantity, providing rapid engraftment so that mortality is well under 5% following high-dose melphalan (200 mg/m²). This treatment can be applied safely to patients even >70 years of age and in the presence of renal failure. Tandem autotransplants after multiregimen induction have yielded CR rates in the 40% range with median durations of EFS and OS of 43 and 62 months, respectively. Certain chromosomal abnormalities (11 and 13; and translocations) represent the dominant adverse prognosticator for EFS and OS, confirmed in over 500 patients including those with prior therapy. Allogeneic transplants, possible in less than 10% of MM patients, are associated with a 50% mortality during the first year and, unfortunately, late relapses; thus, this approach should be reserved for patients with high-risk disease early in their management. A risk-based treatment algorithm that matches a patient’s disease risk with the risk of intervention is presently used, followed by bisphosphonate therapy, not only to delay the onset of MM-related bone disease but also to induce tumor cell apoptosis, indirectly or directly, by down-regulation of cytokines with antiapoptotic activities.

Although many patients relapse, this author subscribes to his mentor’s motto: “Be Prepared for Success!”.

Introduction
The key research principles of cancer biology and therapy were established in acute leukemia by Dr. Emil J Freireich and colleagues in the 1960s and 1970s, using a multifaceted approach to understanding its biology and making cure an objective of therapy once complete hematological normalization had been achieved. Freireich has been credited with having introduced combination chemotherapy (1), an approach that ushered in curative therapy for children and adults suffering from acute leukemia (2-4). Eventually, the concepts of remission induction, consolidation, and maintenance therapy were developed (5, 6). Once a fraction of leukemia patients was cured, Gehan and Freireich (7-9) applied statistical methods to identify prognostic parameters to evaluate novel and potentially hazardous treatments in patients not benefiting from standard regimens. Multivariate regression models eventually centered on genetic abnormalities, initially recognized on the basis of chromosomal aberrations (10, 11) and, increasingly in recent years, molecular abnormalities (12). Thus, distinct entities of leukemia are now defined according to molecular characteristics. Freireich’s enormous contributions included his recognition of the importance of supportive care, which included the introduction of blood cell component support to lessen complications due to infection and hemorrhage (13-17).

Multiple myeloma, on the other hand, had remained an orphan disease in terms of understanding its biology and of improving therapeutic modalities for almost 3 decades since the introduction of melphalan and prednisone brought about some disease palliation. Unlike acute leukemia, myeloma initially presents with less alarming features, and improvement in symptoms can be accomplished with oral administration of melphalan-prednisone in about 50% of patients (18). A fraction of patients will survive more than 10 years without ever attaining a CR (19, 20). Eventually, however, patients succumb to catastrophic illnesses, e.g., renal failure due to hypercalcemia and light chain cast nephropathy, infections, transformation to high-grade lymphoma (like myeloma), or bone marrow failure either due to overwhelming disease or secondary MDS/AML as a
The consequence of chronic administration of alkylating agents (21, 22). Timid efforts to apply the principles of combination chemotherapy at moderate doses, so highly successful in acute lymphocytic leukemia, failed to improve the prognosis of patients with myeloma. Thus, the addition of other alkylating agents, anthracyclines, and Vinca alkaloids did not prolong survival, as attested to by numerous prospective and randomized trials conducted throughout the world (23, 24).

In retrospect, several key flaws in myeloma therapeutic research can be identified, all of which could have been avoided if the lessons of leukemia investigation had been heeded. These include the lack of investigation of the bone marrow in the old days as part of the diagnostic work-up to gain better insight into disease biology; the “satisfaction” of myeloma investigators with palliation, thus avoiding the challenge to evaluate whether more marked tumor cytoreduction, resulting in a sufficiently high incidence of CR, would be a key step toward long-term disease control and cure as in any other systemic malignancy; and, finally, almost an obsession with permutations of similar equitoxic regimens trying to prove or disprove that melphalan-prednisone was no worse than combinations of agents administered at low doses and with minimal efficacy when tested as single agents in refractory disease.

**History of Change**

Chemotherapy research for leukemia and other malignancies typically has followed certain principles that included evaluation of any given agent at maximum tolerated doses. This approach had not been undertaken in myeloma until the development of the VAD regimen that incorporated continuous infusions of vincristine and doxorubicin to expose slowly cycling myeloma cells to presumably effective concentrations during a large part of their life cycle, whereas the glucocorticoid dexamethasone was given in high doses in a pulse fashion of 40 mg in blocks of 4 days spaced 4 days apart to allow recovery from anticipated profound immunosuppression (25). Concern for immunocompromise due to the underlying disease and further aggravation by high-dose dexamethasone led us to refrain from using myelosuppressive doses of doxorubicin to avoid the coincidence of profound immunosuppression and severe neutropenia, leading to potentially fatal infectious complications. VAD turned out to be profoundly effective in alkylating agent-refractory myeloma, affecting more marked and rapid tumor cytoreduction than had ever been reported previously (25). When tested as primary therapy, the incidence of CR (using stringent criteria) did not exceed 5%, and median survival averaged 3 years, disappointing results for a regimen that had been effective in salvaging about one-half of patients with refractory disease (26, 27). We later learned that there was a hierarchy in myeloma phenotypic development. Immature clonal B cells produce interleukin 6, which has since been recognized as an important antiapoptotic signal that also interferes with dexamethasone-induced tumor cell kill, whether produced in autocrine or paracrine fashion (28). Thus, VAD effectively decimated the dominant more mature and less proliferative tumor cell compartment but had little effect on the precursor pool refeeding mature myeloma cells, therefore resulting in failure to improve response duration or survival (29).

A major advance in myeloma therapy was the truly heroic trial by the late Tim McElwain from the Royal Marsden Hospital who administered a single high dose of melphalan i.v. (140 mg/m²) without hematopoietic stem cell or growth factor support (30). Of nine patients treated in this fashion with either refractory myeloma or high-risk untreated disease, true CRs were obtained in five patients. This observation ushered in an entirely new era of alkylating agent dose intensity trials, especially once we introduced autologous bone marrow support (ABMT) to improve the safety even of myeloablative therapy with added TBI, by limiting the duration of potentially fatal bone marrow aplasia to a manageable duration of approximately 2 weeks (31, 32). We reasoned that myeloma as a bone marrow-derived hypoproliferative malignancy (33, 34) was ideally suited to investigate whether net benefit could be derived from high-dose therapy despite reinfusion of tumor cells which, for practical purposes, are not clonogenic because so many previous efforts had failed to generate permanent myeloma cell lines from primary bone marrow samples. Long-term results from these early trials, mainly for refractory disease, indicate that at 10 years, 20% of patients remain alive, and 10% are event-free using melphalan 140 mg/m² and TBI at 850 cGy (Fig. 1; Refs. 35 and 36).

A major milestone toward the routine use of high-dose therapy in myeloma was the observation by Gianni et al. (37) that the use of high-dose cyclophosphamide-mobilized PBSCs instead of ABMT shortened the duration of marrow aplasia markedly so that critical neutrophil levels of 500/μL were typically obtained by days 8–12 and a platelet count exceeding 50,000/μL by day 14; thus, the duration of bone marrow aplasia was shortened to 2–4 days, especially in patients with no more than 1 year of prior chemotherapy (38). Treatment-related mortality decreased to well under 5% (39) and, as a result, a flurry of clinical trial activity ensued to tackle the myeloma problem in earnest.
Affecting PBSC Collection

Significantly faster granulocyte and platelet recovery to critical levels of 500/µL and 50,000/µL, respectively, with the use of mobilized PBSCs as opposed to ABMT. This was true both for patients with no more than 1 year of prior standard therapy (results shown) and for those with more extensive prior therapy (data not shown).

ABMT versus PBSC Transplants and Variables Affecting PBSC Collection

PBSCs collected after HDCTX and GM-CSF (and more recently with G-CSF) provided significantly faster neutrophil recovery than ABMT, regardless of the duration of prior therapy; significantly more rapid platelet recovery was noted with PBSCs among those treated for no more than 12 months with standard regimens (Fig. 2; Ref. 40).

It is now well established that PBSCs do contain clonal B cells and thus, contrary to traditional thinking, do not represent a preferred source of hematopoietic stem cells because of less tumor cell contamination (41, 42). Recent data indicate that, in the process of PBSC procurement with HDCTX, myeloma cells are mobilized as well, however, with a time delay of several days (43). Thus, even without removal of tumor cells by selection for CD34⁺ (41) or CD34⁺/Thy-1⁻/Lin⁻ cells (42), normal hematopoietic progenitor cells can be enriched if collection of PBSCs can be completed within the first 2 days of apheresis, which is facilitated by processing large volumes (≥15 L) of blood. It is now generally held that at least 2 x 10⁶ CD34 cells/kg body weight are required for the safe conduct of PBSC transplants (38).

Using CD34 antigen expression as a surrogate marker of hematopoietic stem cell function, prolonged duration of standard therapy, especially with melphalan and nitrosourea, targeting primitive hematopoietic precursor cells, markedly impairs the ability of PBSC collection and compromises hematopoietic engraftment after myeloablative therapy (Fig. 3; Refs. 38 and 40).

The recent observation that adequate PBSCs can be collected with high-doses of G-CSF alone at minimal toxicity has resulted in abandoning HDCTX for PBSC mobilization because of its more profound toxicity and relatively limited antmyeloma activity (44, 45). Thus, although large quantities of CD34 cells (>5 x 10⁶/kg) can be procured in a higher proportion of patients with HDCTX, recoveries of granulocytes and platelets to critical levels of 500/µL and 50,000/µL, respectively, are entirely comparable whether or not HDCTX was added to G-CSF (Fig. 4).

Data on Phase II Studies with Autotransplants

Table 1 summarizes the results of nine Phase II trials containing at least 50 patients (40). Patient and treatment heterogeneities are readily apparent, and only three studies were analyzed on an intent-to-treat basis. Collectively, these data, however, demonstrate that, with the use of PBSCs, 60-day

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Thus, two cycles of melphalan (200 mg/m²; MEL 200) were even at diagnosis. Rather than increasing the intensity of a single GM-CSF for PBSC collection, and subsequently etoposide/cause of its speed of tumor cytoreduction without inflicting CR, and median durations of EFS and OS are on the order of 3 months, respectively, with a median CR duration of 54 weeks. The key pretreatment prognostic factor for both EFS and OS was the absence of unfavorable cytogenetics, i.e., abnormalities of chromosomes 1/1 and 13/13 (48). Progression by greater than 25% during induction. IFN maintenance was offered to all patients after two transplants. Despite the complexity of this “total therapy” program, 84% completed one and 71% two transplants within 8 and 15 months, respectively (47). Throughout all phases of therapy, PR and CR rates increased progressively and reached 81 and 38%, respectively, at the time that two transplants were to have been conducted (intent-to-treat); among the 164 patients actually completing two transplants, PR and CR rates of 94 and 48% were achieved. Median durations of EFS and OS have been reached at 43 and 62 months, respectively, with a median CR duration of 54 months. The key pretreatment prognostic factor for both EFS and OS was the absence of unfavorable cytogenetics, i.e., abnormalities of chromosomes 11 and 13 (48). This tandem transplant approach had been piloted in previously treated patients prior to its incorporation into the comprehensive treatment of newly diagnosed patients (“total therapy”; see above; Ref. 49). Such tandem transplants have now been offered to 542 patients who have had at least 6 months of follow-up; median durations from first transplant of EFS and OS were 26 and 47 months, respectively (40, 50). Absence of “unfavorable karyotypes” (11/13 abnormalities and presence of any translocation), low β₂-microglobulin levels ≤2.5 mg/L and ≤12 months of standard therapy emerged as the key features associated with superior outcome, so that distinct risk groups could be identified, aiding in the selection of high-risk patients for novel interventions (Fig. 5; Ref. 51).

### Comparative Trials

The notoriously poor outcome with standard therapy motivated most myeloma investigators to perform pilot trials of high-dose therapy with autotransplants, which effected marked tumor cytoreduction with CR rates in the 20–40% range. The IFM recently reported results of a prospective randomized trial, comparing VMCP/VBAP (standard therapy) versus ABMT with 140 mg/m² melphalan plus 800 cGy TBI after four cycles of induction therapy with VMCP/VBAP (52). Superior results in terms of CR rates as well as EFS and OS were observed among the 100 patients randomized to transplant versus those receiving standard therapy, although ultimately only 74 patients were actually transplanted (Fig. 6). Another French group compared early versus delayed transplantation and noted comparable survival in both groups, although patients assigned to initial myeloablative therapy enjoyed significantly superior CR rates and longer EFS (53). The Arkansas group performed a pair-mate analysis of a subgroup of their “total therapy” program of 116 patients (no prior therapy, minimum follow-up of 18 months), who were matched for age, β₂-microglobulin and creatinine (the critical prognostic variables with standard therapy), with 116 patients receiving mainly VAD as part of Southwest Oncology Group trials (54). As with the IFM trial, superior remission rates and significantly longer EFS and OS were observed among transplanted patients (intent-to-treat). In fact, probably due to greater dose intensity with two transplants, the CR rate of 40% was almost twice the 22% after one transplant in the IFM study, and the median EFS of 49 months with “total therapy” exceeded the 27 months on the single transplant arm of the French study. The seemingly greater tumor cytoreduction after a tandem transplant prompted the subsequent IFM-94 trial, randomizing patients between one and two transplants.
preserved renal function; specifically, early mortality remained

dialysis, and the outcome was not different from those with

among patients with renal failure (56), excluded from high-dose therapy trials. Once we demonstrated

of prior therapy were accounted for (Fig. 7).

Salvage Therapy for Posttransplant Relapse

"Life after relapse post-transplant" is an important concern

to patients and their physicians alike (58). We had the oppor-
tunity to examine the outcome of 196 patients who had relapsed,

including 91 after a scheduled tandem transplant (59). Although

not studied prospectively, a treatment algorithm was used that is
delineated in Fig. 8. Eventually, 63 of 105 patients relapsing

after a single transplant and 19 of 91 relapsing after a tandem

transplant received an additional transplant regimen. Ten per-
cent died within 2 months, 8% achieved CR, and postsalvage

EFS and OS were 8 and 14 months, respectively. EFS and OS

were longer with primary salvage transplant and low presalvage

β₂-microglobulin ≤2.5 mg/L. Using these two variables, the

best outcome was noted among 25 patients exhibiting both

favorable features as opposed to the 76 with one and 95 patients

with two unfavorable parameters. The respective CR rates were

32, 7, and 3%; EFS and OS durations were 64+, 15, and 9

months, respectively (all P = 0.0001). Thus, posttransplant

relapse should not be considered as ultimate treatment failure.

Patients with only one prior transplant definitely benefit from the

administration of further high-dose therapy, which is in line

with our current practice of a scheduled tandem transplant

within 6 months. Indeed, we always assure that additional

PBSCs are available for all patients whether transplanted once

or twice, so that further salvage therapy including myeloablative
treatment remains a treatment option.

Posttransplant MDS/AML

Recent studies in Hodgkin’s disease (60) and non-

Hodgkin’s lymphomas (61) suggest a possible induction of

MDS/AML after autotransplant. Among 188 patients with my-
eloma with a minimum follow-up of 24 months after transplanta-
tion, 7 patients developed cytogenetic and/or morphological evidence

of MDS/AML, all among the 117 patients with ≥12 months of prior therapy, for a projected incidence of 12% at 48 months; by

contrast, none of the 71 patients receiving “total therapy” with stem cell-sparing induction therapy developed leukemia (62).
Allogeneic Transplants

Allogeneic transplants offer the advantage of lack of tumor cell contamination and, as demonstrated recently, of a GVM effect (63, 64). In light of an unfortunately high treatment-related mortality with allotransplants, consistently in the 50% range within the first year (65–67), the issue of both short- and long-term prognosis after allogeneic versus autologous transplant has been raised. Results of a retrospective case-matched study from the EBMTR involving 189 autologous and 189 allogeneic transplant patients revealed significantly superior outcome among the autologous group with a median survival of 34 versus 18 months, mainly due to allotransplant-related mortality of 41% versus 13% among autotransplant recipients (68). Progression-free survival was not superior after allogeneic transplants because of comparable rates of relapse and progression with both modalities. In a pair-mate analysis of 63 patients, we observed superior EFS and OS of 27 and 48 months after autotransplants compared to 8 and 10 months, respectively, after allogeneic transplants, mainly due to a considerably higher mortality in the first 60 days of 25% with donor transplants as opposed to 2% with autotransplantation (40).

Conclusions and Future Directions

Myeloma is best characterized by its resistance to presently available treatment modalities, probably as a result of complex genetic abnormalities, all conferring a survival advantage to myeloma cells. Clinical trials using randomized concurrent or historical controls both demonstrate that “more is better,” even to the point of tandem transplants, which can be performed safely in patients up to age 70 and with renal failure (when using melphalan ± TBI), with a transplant-related mortality of well under 5%. Work in progress will shed light on the importance of early versus delayed transplantation (North American Intergroup Trial 141), double versus single transplant (IFM-94 study), and on the use of CD34 selection as a means of reducing the likelihood of tumor cell reinfusion in the process of autologous transplantation. The demonstration of certain cytogenetic abnormalities conferring poor outcome along with standard variables such as β2-microglobulin, C-reactive protein, and others affords a risk-oriented treatment approach (40). Thus, we are offering “standard tandem transplants” to good-risk patients, whereas poor-risk patients require innovative therapy. Considering myeloma biology, it is our contention that autograft decontamination of tumor cells through either positive selection (41, 42) or removal of tumor cells by monoclonal antibodies (69) and/or cytotoxic agents will only benefit the best-risk group, in whom marked and sustained reduction in tumor burden can be achieved through high-dose therapy and in whom hence reinfusion of tumor cells may become clinically relevant. It is now possible, through the use of PCR technology (70), to better monitor for minimal residual disease and “molecular CR” beyond standard hematological and biochemical indicators of CR (71). Presently, ongoing trials with CD34+ (41) or CD34+/Thy-1−/Lin− selection (72) do indicate their feasibility in principle; however, early relapses have been noted, even in minimally pretreated patients, and delayed recovery of granulocytes and especially of platelets as well as profound immunosuppression, when compared to nonselected PBSCs, do raise some caution (73). Strategies to reduce the risk of postautotransplant relapse may include maintenance chemotherapy, with regimens found to be highly effective in the setting of salvage therapy after autotransplants, such as dexamethasone/cyclophosphamide/etoposide/cisplatin (7, 74), immunological manipulations, such as idiotype (75) or dendritic cell vaccination (76), and the use of haploidentical donor cell infusion at the time of a second transplant to generate a GVM effect, hopefully without serious GVHD, as a result of timely rejection of haploidentical grafts. Finally, the safety of allotransplants needs to be improved so that patients with high-risk myeloma can benefit from a GVM effect (63). This may be accomplished by T-cell depletion to reduce incidence and severity of GVHD; to elicit a GVM effect, a fixed dose of thymidine kinase gene-transduced donor T cells is administered upon completion of hemopoietic engraftment, which can be inactivated by ganciclovir in the case that severe GVHD ensues (77). Other approaches may focus on the generation of idiotype-
specific allogeneic CTLs to avoid GVHD and on means of increasing the immunogenicity of tumor cells by transduction with GM-CSF or other cytokines (78).

An important lesson from standard chemotherapy trial research in myeloma over the past 3 decades is that bold steps are needed to achieve therapeutic gain. Standard melphalan-prednisone or similar approaches should be avoided, especially since the prolonged administration of melphalan and nitrosoureas compromises stem cell reserve and carries a high potential for secondary MDS or AML, which may be aggravated by subsequent autotransplants (63). Local radiotherapy, in our opinion, is often used without considering the problem at hand and long-term consequences. Thus, pain due to the development or worsening of vertebral compression fractures in patients responding to chemotherapy is unlikely to improve with radiation. Furthermore, extensive radiotherapy to bone marrow-containing sites will interfere with PBSC collection and, in the allograft setting, may make TBI impossible although preferred in the setting of T-cell depletion to alleviate GVHD.

We strongly recommend initial treatment with dexamethasone or VAD-like regimens and early PBSC collection in all patients sufficient for two future transplants. In this fashion, patients retain valuable treatment options. Although historically considered as a modality to be used only in the context of curative therapy, recent experience with autotransplants in myeloma certainly attest to their role also for palliation, with a high quality of life obtained (49). The observation of sustained CR in about 10% almost 10 years after autotransplants for advanced and refractory myeloma (36) suggests that cure may be achievable, especially when tandem transplants are performed in a good-risk setting early during the disease course (54).

New agent evaluation has to continue to identify drugs that display greater specificity toward myeloma cells so that eventually rather nontoxic treatments with a prospect for sustained disease control can be offered to multiple myeloma patients as well. Unfortunately, the purine analogues cladribine (2-chlorodeoxyadenosine) and fludarabine, highly effective in the treatment of the lymphoid leukemia (80), turned out to be entirely ineffective in multiple myeloma (81). The ideal scenario for Phase II trials in multiple myeloma is the setting of persistent or relapsing disease after high-dose therapy with hemopoietic stem cell support which, when performed early in the disease course, should result in excellent hemopoietic stem cell reserve so that also potentially myelotoxic agents can be tested.

Rather than providing specific recommendations for the practicing internists, our message is to refer patients to specialists for inclusion in meaningful clinical trials, presently occurring in no more than 5% of patients diagnosed each year in the United States. Especially in the present healthcare climate, it is imperative that available resources be deployed wisely to answer questions that are likely to advance the understanding and treatment of a disease that has defied therapeutic efforts for so long. The reproducibly dismal outcome with standard melphalan-prednisone in the majority of patients should alert patients and physicians alike to the notion that participation in a well-designed clinical research trial should become the "standard approach" because it assures progress in therapy. Such clinical trials must ask sufficiently radical questions to yield biologically and clinically meaningful answers. Specialized centers with comprehensive laboratory and therapeutic research programs are ideally suited to eventually develop more rational therapy aimed at correction of the underlying dysregulation of cytokines and immune responses.

Personal Tribute

I will be forever indebted to Emil J Freireich for his unique approach to the treatment of cancer that challenges dogma, clinical and basic research, asks sufficiently radical questions using appropriate (i.e., not necessarily randomized) clinical trial techniques, and puts each and every patient’s long-term prognosis first. As a result, in my clinical practice, I have learned to capture as much as possible about an individual patient’s tumor and host cell characteristics so that the plan for cure can be designed that avoids, in presently seemingly incurable malignancies, interventions that would compromise future curative therapeutic options. Dr. Freireich’s guidance is felt in my daily patient care and clinical research endeavors. I wish him many more years of provocative contributions to the field of oncology and medicine.

References


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