

Lessons Learned from Treating Older Multiple Myeloma Patients with Novel Agents

The standard of care for treating symptomatic multiple myeloma for the past 10 years or more has been induction chemotherapy (CT) followed by consolidation with high dose chemotherapy and autologous stem cell transplant (ASCT). This protocol was based on strong clinical trial data from France in 1996 and England in 2003 showing improvement in response rates (ORR), progression-free survival (PFS) and overall survival (OS) when compared to standard chemotherapy without transplant¹. PFS ranged from 25-42 months and OS from 4-5 years². Approximately one-third of transplanted patients were alive at 10 years³.

Based on these data, ASCT remained the standard of care until the recent publication of quite similar response rates and long-term survival statistics when older myeloma patients were treated only with chemotherapy and novel new drugs without ASCT. Therefore, the timing of transplant has been reevaluated and the question raised: should all patients, regardless of age, be treated first with chemotherapy and /or novel agents and the transplant procedure reserved instead for salvage at the time of relapse? This question remains unanswered today but is the subject of intense clinical research.

The Age Factor

Almost all important randomized clinical trials used to establish ASCT as the standard of care were performed in patients 65 years or younger, and before the introduction of novel agents. Until recently, ASCT was not an option for myeloma patients older than 65. This meant that only 35% of cases qualified, because the median age at diagnosis is 70; 37% actually present at 75 or older⁵. As the treatment-related mortality for ASCT declined to only 1-2%, which is about the same as standard chemotherapy regimens, some transplant groups have liberalized the age cut-off and accept selected patients up to age 75 or more, based on physiologic rather than chronologic age. If there are comorbidities, or age is greater than 75, reduced dose transplant chemotherapy preparatory regimens usually are used⁵. Nevertheless, there is still no substantial data to support up-front ASCT as the standard of care in older patients. In one important early trial, ASCT failed to show any benefit for older patients ages 65-75; overall survival for chemotherapy plus thalidomide was 51.6 months compared to 38.3 months for ASCT⁴.

Even in trials enrolling mainly younger patients, 4 of 7 recently published randomized trials comparing transplant to chemotherapy found that despite better ORR, CR, and PFS with transplant, the overall survival was similar¹. Publication of these data has caused many experts to consider revising the usual guidelines for the standard of care.

Risk Stratification

Although cases of myeloma may present in similar fashion and the malignant plasma cells appear the same under the microscope, the disease is very heterogeneous. The biological activity of myeloma varies from aggressive with short survival to indolent and a lengthy survival. If possible, it is important to risk stratify patients at time of diagnosis in order to predict the natural history and properly tailor therapy. Adverse prognostic factors include a high β 2 microglobulin, low albumin, lambda light chains, high LDH, significant renal insufficiency, IgA paraprotein, and if available a plasma cell labeling index > 3% (PCLI).

Notwithstanding the usefulness of these predictive markers, there is growing appreciation that the primary driver of multiple myeloma is genetic. High risk patients are increasingly being identified as those with cytogenetic del 13 or hypodiploidy, and by FISH del 17p, t(4;14), and t(14;16). Other genetic abnormalities seemed not to have an adverse effect on prognosis. Thus, all patients should undergo metaphase cytogenetics and FISH analysis prior to selection of treatment, because the results are likely to influence the choice of therapy, including ASCT⁶.

Options for Non-Transplanted Patients

Until the late 1990s the standard of care for symptomatic myeloma was one of three regimens: melphalan and prednisone (MP), vincristine, adriamycin, dexamethasone (VAD), or high dose pulse dexamethasone (DEX) alone. MP was easier to administer, less toxic and yielded objective ORR in 31 to 48% of cases, CRs in 1-4%, PFS 14-18 months, and

overall survival averaging 27-47 months depending on disease aggressiveness⁷. The ORR was approximately 43% with DEX and 55% with VAD; OS with VAD was 25 months for aggressive and 40 months for intermediate and low volume disease⁸.

This was the situation for more than two decades until thalidomide was introduced. When thalidomide (T) was moved from salvage to up-front therapy and combined with standard MP, much improved outcomes were reported. The response rate increased to 60-76% with 13-16% complete responses; PFS ranged from 24-28 months, and OS from 37-52 months⁵. Lenalidomide (Revlimid) (R), a derivative of thalidomide with less neurotoxicity was introduced in 2004, and when combined with standard MP proved to be a breakthrough in the treatment of myeloma. This combination, MPR, produced responses in 81% of patients with 24% complete; PFS was 28.5 months and 91% treated patients are surviving at 2 years. The best results occurred if lenalidomide was continued as maintenance after the initial cycles⁹. The combination of lenalidomide and either high or low dose dexamethasone (RD or Rd) also produced similar 2 year results, although the low dose regimen was less toxic.

More dramatic improvements were forthcoming after bortezomib (Velcade) (V) was approved by the FDA in 2003. This drug is the first in an entirely new class of drugs, designated proteasome inhibitors, to be used for therapy of myeloma. When used as up-front therapy and added to MP (VMP) or MPT (VMPT) the ORR was 79 and 86% with CRs 21 and 34% respectively. At 2 years 58% of VMP and 70% of VMPT cases have not progressed and 89% of both groups are surviving. Furthermore, randomized trials with a variety of other regimens like VT, VTP, C(cytoxan)TD, and reduced intensity autologous transplantation are examples of protocols currently being studied in an attempt to discover even better combinations.

Unanswered Questions

It is unknown if the markedly improved ORR, CR, and PFS noted with bortezomib (V) and lenalidomide (R) regimens will translate into similar or better survival results than MPT, or autotransplant regimens. Currently, regimens including these two drugs produce the best early outcomes⁵, but only 2 year follow-up data are published. Long-term survival data is available only for MPT, and the outcomes reported are approximately equal to those achieved in younger patients undergoing autologous stem cell transplant^{1,5}.

Many experts contend that achieving a CR or very good PR (VGPR) correlates with a better outcome and therefore is a reasonable goal for therapy. However, most evidence indicates that this applies to high risk and probably intermediate risk patients; it is less certain that a CR or VGPR is necessary to improve the outcome of low risk patients⁶. Also, recent studies show that maintenance therapy improves PFS, and although studies are inconsistent, some have reported that CR/VGPR rates also may increase during maintenance. Nevertheless, it has not been established with certainty that improved responses with maintenance therapy will automatically translate into better survival. There are no large studies of maintenance therapy in older patients, nor are there clear guidelines on how long it should be continued⁷.

Bortezomib (V) therapy not only has been very successful, but it has also added a new dimension to treatment. It has been demonstrated to be more effective in high risk patients than other agents. Bortezomib seems to overcome the negative prognosis associated with unfavorable genetics, although the number of patients studied in this respect is relatively small and the duration of follow-up still fairly short². In addition, bortezomib (and thalidomide) can be administered without dose reduction to patients with myeloma kidney and renal failure providing an important new option for dealing with this usually serious complication. However, it is still uncertain that regimens with bortezomib improve long-term survival.

References

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This publication is a review and not meant as a guideline for medical treatment.