

Novel agents in myeloma: an exciting saga

by Morton Coleman, MD

An exciting page in the annals of cancer therapy has been unfolding recently with the development of novel agents for the treatment of multiple myeloma. Less than a decade ago, myeloma therapy was in the doldrums, and had been that way for years. Other than bisphosphonates, basic therapy consisted of alkylating agents in all their various guises, although oral melphalan and to a lesser degree, cyclophosphamide were the mainstays of treatment. Combining alkylating agents into a triple therapy combination had been considered a step forward by some, but, in actuality, represented simply more intense therapy. Steroids, particularly high dose dexamethasone, were helpful, but the contribution of vincristine and doxorubicin in the classic VAD program was marginal. Autologous transplantation, employing mostly high dose alkylating agents, for younger patients was and still remains the gold standard therapy, but its impact over conventional chemotherapy is modest and it does not represent curative therapy. Further, it is not applicable to a large cohort of patients, the elderly, who predominate in this disease. Median survival for active myeloma a decade ago ranged from three to five years.

In the late 1990's, an assemblage of a determined and insistent wife of a heavily pretreated myeloma patient, a receptive and innovative group of physicians in Arkansas, and a biotech company came together to provide the first major breakthrough in years. Thalidomide, the infamous drug used as a sedative in pregnant women responsible for shortened or truncated limbs in newborns, was tried in myeloma for its putative anti-angiogenic properties based on the observation that the more aggressive or advanced the myeloma, the greater the vascularity. As is almost universal in cancer therapy, end-stage, refractory, or previously treated patients were the initial recipients of this novel therapy. Indeed almost all of the patients had received extensive treatment and had limited marrow reserve. Despite these severe drawbacks, thalidomide produced responses in approximately a third of patients although some of the responses were minor (the myeloma immunoglobulin levels declined by less than half). Thalidomide though was particularly useful here because it is minimally myelosuppressive. Subsequently several

groups, including ourselves at Cornell, observed that the addition of steroids greatly augmented the therapeutic effect of thalidomide in previously treated patients enhancing both the quality and amount of the responses. Successful responses occurred in well over half the patients. Our program at Cornell gave thalidomide only in low dose, dexamethasone once weekly, and added clarithromycin. Responses approached ninety percent. Whether the enhanced response in our program reflected differences in patient selection (one of many problems in comparing Phase II results), the effect of clarithromycin on the myeloma or the metabolism of the other two drugs, or the use of once weekly high dose dexamethasone is unclear. Once weekly high dose (referred to as “low dose”) dexamethasone though has been proven superior to the “classical” Barlogie method of spaced four continuous days of high dose dexamethasone. While steroids combined with thalidomide greatly augmented the response, there is no such thing in life as a free lunch. So was the situation here. The steroids also ratcheted up the toxicity. Indeed the major impediment to the long term use of thalidomide has been neuropathy which invariably occurs in almost all individuals receiving the combination. The neuropathy does not resolve easily even with cessation of the drugs. In addition, we, and subsequently others, observed that the combination was associated with an extraordinarily high incidence of thrombosis and sudden death. Reasoning that thalidomide may produce vascular injury if it is truly antiangiogenic, low dose aspirin was inaugurated by us and proved successful notwithstanding the reported lack of efficacy of aspirin in “slow flow” venous thrombosis, a frequently reported phenomenon with thalidomide-dexamethasone. Heparin and warfarin have also been effective, but low dose warfarin may not be adequate.

As a natural sequence in testing, the Mayo Clinic headed up a cooperative group study pitting thalidomide and dexamethasone in a randomized trial against dexamethasone alone in newly diagnosed patients destined for autologous transplantation. The combination is, in some ways, ideal since neither medicine of the combination was myelosuppressive. The combination indeed proved superior to dexamethasone alone producing statistically superior responses (70% versus 50%) but at a cost of greater toxicity, primarily thrombotic events. Unfortunately antithrombotic measures were not employed in the study.

Following the remarkable success of thalidomide, two novel agents, bortezomib and lenalidomide, followed in relatively rapid succession.

Lenalidomide, an IMiD (immunomodulatory drug) reportedly more potent than thalidomide, was introduced in 2006. Again treatment was first tried in previously treated patients. As with thalidomide, approximately a third of patients responded. Two concurrent randomized studies, one spearheaded in North America by the M.D. Anderson group and one in Europe, Australia and Israel, tested lenalidomide and dexamethasone against dexamethasone in previously treated patients. Combined dexamethasone and lenalidomide was superior and produced responses, as with thalidomide, in approximately half of patients. Once data of the combinations efficacy were established in previously treated patients, newly diagnosed patients were studied. Responses in at least 90% of the patients were produced. In addition, depending on the nuances of the combination (such as the addition of clarithromycin or the use of weekly dexamethasone) or response criteria used, i.e., strict complete remissions, complete remissions, near complete responses, or very good partial responses (all connoting at least a greater than ninety percent reduction in immunoglobulin), up to 40% of patients had nearly a complete reduction of the myeloma spike. These responses represented a significant achievement since responses of this magnitude were rarely seen with conventional chemotherapy, and were equal to or superior to transplantation. Data suggest that these major responses may translate into enhanced survival. Remarkably thrombosis was less problematic with the prophylactic use of antithrombotic agents; however, thrombosis was seen when the antithrombotic agent and lenalidomide were discontinued simultaneously. Apparently any damage to the endothelium is more long-standing than the antithrombotic effects of aspirin, for instance, which usually abates in about ten days.

Bortezomib, another novel agent, entered the market in 2003 with a mechanism of action thought to be entirely different from the IMiDs. Putatively bortezomib inhibits proteasome activity allowing inhibition of NF-kappa B, a substance with many nefarious activities once it enters the nucleus. Other mechanisms though may be operative. Nevertheless similar to the results with thalidomide and lenalidomide, responses in previously treated patients hovered around a third. Adding steroids clearly enhanced the efficacy of bortezomib. When used in previously untreated patients, with augmentation by necessary steroids, responses similar to the IMiDs were obtained. Nearly 90% of patients responded, again with major responses. In a large randomized study headed by the Dana Farber in Boston, bortezomib when tested against dexamethasone was clearly superior and showed an actual enhancement in survival. Bortezomib, like

thalidomide, produces neuropathy, although the neuropathy is clearly different from thalidomide and is more rapidly reversible. Like lenalidomide, there is some myelosuppression, primarily thrombocytopenia, but generally less than with lenalidomide. The IMiDS are taken orally, bortezomib is given intravenously. Bortezomib though need not be given on a continuous basis once a major response has occurred and been sustained.

Given the different mechanisms of action, the novel agents have been combined, but because of overlapping toxicity, doses may require attenuation. For instance, thalidomide has been combined with bortezomib but suffers from overlapping neurologic toxicity. Bortezomib and lenalidomide are also being combined, but do have some overlapping hematologic toxicity. A thalidomide and lenalidomide combination represents another possible combination due to the relative lack of overlapping toxicity. Whether such a combination will have an additive or synergistic impact remains to be seen, since there are insufficient data to indicate that resistance to one will not impart resistance to the other. The preliminary responses though to combinations of the IMiDS with bortezomib in previously treated patients look remarkably impressive. Now that doses have been finalized, it is only a matter of time before results of the combinations will be forthcoming in both treated and newly diagnosed patients.

The group in Los Angeles, as well as the Europeans, the Italians and French in particular, took a different tack. They combined novel agents with chemotherapy, and showed enhanced efficacy to chemotherapy alone. The Italians have shown that thalidomide combined with melphalan was clearly superior to melphalan alone. The French have shown in newly diagnosed elderly that thalidomide and melphalan combined were clearly superior to melphalan alone or to a reduced intensity autologous transplantation. Meanwhile the group formerly at the Cleveland Clinic showed that pegylated liposomal doxorubicin was effective in myeloma despite what appears to be marginal activity of standard doxorubicin. The group in North Carolina, having done pioneering work with bortezomib, noted excellent results combining bortezomib with liposomal doxorubicin. Dr. Harousseau, leading a French cooperative group compared combined bortezomib and liposomal doxorubicin to bortezomib alone in previously treated patients. The results with the combination were superior in just about every parameter measured. It is now apparent that combinations of novel agents with

themselves, steroids and/or chemotherapy are superior to a novel agent, steroids, or chemotherapy alone and probably represent true synergism.

A question often posed is which novel agent is superior and which should be used initially. In point of fact, the data would suggest they are all of relatively equal efficacy, and that the selection of the particular agent should be based on the necessities presented by the patient. Does the patient have a thrombotic tendency, renal failure, a karyotypic chromosome 13 abnormality, an access problem, neuropathy, or limited marrow reserve? In each of the aforementioned presentations, one novel agent over the other would be selected.

The critical issues currently are what role will novel agents play in transplantation. Will they make transplantation more effective or will they turn myeloma into a chronic disease obviating the need for transplantation. Most importantly, have they improved the overall survival of myeloma patients? While some data are available and some are currently being culled, the answer appears to be a resounding yes.

Only several handfuls of institutions, countries, and studies have been mentioned, but to be certain there have been many other institutions throughout the world and many other pertinent studies that have contributed to our better understanding of these remarkable new agents. Indeed there is now a bewildering array of trials combining and using novel agents with themselves, steroids, and chemotherapy, and many other new agents are rapidly coming down the pike. It is an exciting time to be engaged in myeloma therapy.