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EDITORIAL

The Era of Combination Therapy in Myeloma

Sagar Lonial and Jonathan L. Kaufman, *Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA*

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For decades, there have been numerous debates and clinical trials that have evaluated the utility of sequential single-agent anticancer therapy versus a more intensive combination approach for patients with a variety of solid tumors and hematologic malignancies. The optimal treatment approach is dependent on the tumor type, as well as the potential for synergistic enhancement of tumor apoptosis when agents are combined as opposed to being used in a sequential, single-agent fashion. Optimal use of combination therapy presumes improved clinical outcomes in the context of safe and tolerable delivery of therapy. Diseases such as diffuse large-cell lymphoma, testicular carcinoma, follicular lymphoma, and chronic lymphocytic leukemia are examples of diseases for which combinations of agents are more effective than sequential single agents, whereas in the setting of metastatic breast cancer or non–small-cell lung cancer, sequential single agents are often used to minimize toxicity. In the treatment of patients with multiple myeloma, this debate has been renewed of late as a consequence of an improved understanding of disease biology coupled with the availability of new and highly active agents. The net result has been a series of cure versus control debates, with each side espousing the virtues of its approach while demonizing the attributes of the other, yet the real data that are needed to address this question have not been fully available to adequately settle the debate. In the article that accompanies this editorial, Garderet et al[1] present data from a phase III trial that compares the combination of bortezomib/thalidomide/dexamethasone (VTD) with thalidomide/dexamethasone (TD) for patients with relapsed myeloma. Garderet et al clearly demonstrate that the use of combination therapy results in heretofore unprecedented improvements in progression-free survival (PFS) for patients with relapsed myeloma.

The earlier reluctance to use combination therapy in multiple myeloma stems from data that were published in the 1990s, in which the use of combination regimens for newly diagnosed patients were evaluated in comparison with what was then the standard treatment, melphalan/prednisone (MP). In large retrospective analyses, it was demonstrated that while combination treatments did improve response rates, ultimately, they were too toxic and had too little biologic activity to warrant their use compared with the simple and less toxic MP regimen.[2] An alternative interpretation of these data is that both approaches were equally ineffective. Although the use of MP for younger patients has now been supplanted by the use of high-dose melphalan and autologous transplantation,[3] the concern about the use of combinations remains. However, use of agents that are more recent additions to our antimyeloma armamentarium, such as thalidomide, bortezomib, and lenalidomide, has radically changed the approach to induction therapy.[4] In a series of patients from our group, the use of VTD among newly diagnosed patients demonstrated a high overall response rate, and this was noted among both patients with standard and high-risk genetics.[5] A subsequent phase III randomized clinical trial by Cavo et al[6] solidified the benefit for combination therapy when VTD was demonstrated to be superior to TD as measured by overall response rate, depth of response, and post-transplantation PFS among newly diagnosed patients. More importantly, the use of combination therapy overcame the poor outcomes for patients with overexpression of *FGFR3* as defined by the t(4;14) cytogenetic abnormality, and did lessen, although did not completely mitigate, other poor genetic–risk sets. Additionally, the use of combinations in the first-line as well as post-transplantation setting induced molecular responses in a subset of patients, many of whom have enjoyed long durations of treatment-free remission.[7] These data suggest that combination therapy should become a standard for newly diagnosed patients if our goal is to more effectively treat high-risk disease and provide optimal post-transplantation responses. However, this approach was not without adverse effects. The use of combination therapy did result in more adverse effects, in particular more peripheral neuropathy, likely as a consequence of concomitant use of thalidomide and bortezomib. However, Richardson et al[8] have demonstrated that replacing thalidomide with lenalidomide to form the lenalidomide/bortezomib/dexamethasone regimen not only improved the overall response rate compared with VTD, but also was better tolerated, with less neuropathy. Given the improved outcomes for patients with myeloma, minimizing potential long-term adverse effects is clearly an important goal. Nonetheless, it does seem that combination strategies such as VTD,[6] lenalidomide/bortezomib/dexamethasone,[8] bortezomib/doxorubicin/dexamethasone,[9] and cyclophosphamide/bortezomib/dexamethasone[10] have arrived and are making a major impact on the overall response rate and post-transplantation outcomes compared with older chemotherapy alone or doublet combinations for newly diagnosed patients with myeloma, signaling the arrival of combination therapy for newly diagnosed patients.

However, does the same logic apply for patients with relapsed disease? Patients with relapsed myeloma are often sicker, carry with them some of the residual effects of their initial therapy, and historically have a shorter duration of response. Thus, the rationale for combination therapy has been less clear in this disease setting. Clinical studies have demonstrated that the use of bortezomib alone[11] or lenalidomide/dexamethasone[12,13] is superior to high-dose dexamethasone alone. The addition of liposomal doxorubicin to bortezomib improves PFS among a group of bortezomib-naive patients, from 6

months to 9 months,[14] but to date, the maximum benefit from large phase III randomized trials in the relapsed setting is less than 12 months. This is why the article by Garderet et al[1] is of such critical importance. Compared to the PFS seen in the single-agent trials described, the PFS for the VTD arm was 19 months, rendering this the longest PFS reported by a phase III trial among patients with relapsed myeloma, and again highlighting the importance of combination therapy. Was the use of three-drug therapy of universal benefit? Clearly the overall response rate and durability of response is quite high, but what about issues of toxicity? In this experience, the use of full-dose thalidomide and bortezomib did result in a high rate of grade 3 neuropathy, an adverse effect that many patients will carry with them for the remainder of their lives and which can have a significant impact on quality of life. What is the optimal duration of therapy to maximize responses and response duration without the emergence of such irreversible or intolerable adverse effects? The use of lower doses of either or both agent has been shown in phase III trials to result in comparable efficacy with less neuropathy, and more importantly, we now have alternative schedules[15] (weekly bortezomib) and administration routes[16] (subcutaneous) that have been shown in phase III trials to reduce the incidence of bortezomib-induced neuropathy. The use of lenalidomide in lieu of thalidomide is also better tolerated and has been shown in trials to be effective, although it has not been tested in the context of a phase III trial for patients who have experienced relapse. Finally, there are newer agents on the horizon, such as carfilzomib[17] and MLN9708,[18] both of which have less neuropathy associated with their use and may provide safer and more effective options in the near future.

From large randomized trials, we now have clear evidence that combination therapy is superior to doublets among both newly diagnosed patients and those experiencing relapse. Taking a biologic perspective on treatment, combination therapy allows for more rapid and deep responses, overwhelms potential resistance, attacks a tumor at the time of greatest drug sensitivity, and allows for synergistic combination effects to occur between targeted agents, which would not occur if drugs were given sequentially. These effects have achieved levels of flow cytometric or molecular remission that were previously observed only for patients with myeloma who were undergoing the more toxic and morbid procedure of allogeneic transplantation. It is time to declare this the era of combination therapy for patients with myeloma. It is now clear that combinations are highly effective at achieving reduction in disease burden and improvement in PFS for patients with multiple myeloma. Given the relatively short follow-up of the trial reported by Garderet et al,[1] it is perhaps unrealistic to expect that combination therapy would have already resulted in improved overall survival, although this is an important consideration as well. Nevertheless, current attention should be focused on determining how best to optimize combination therapy for patients on the basis of biologic and risk-based assessments. Rather than asking the combination-or-not question, perhaps we should now ask which combination is best for any given biologic subset. Only through careful genomics or genetics-based interrogation of the data will we ultimately be able to define the ideal therapy for a given patient.

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