Bortezomib in newly diagnosed multiple myeloma

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Preclinical studies have shown that, in addition to showing anti-multiple-myeloma activity as single agents, new agents such as bortezomib also enhance the efficacy of chemotherapy and steroids. A randomised trial has now established that bortezomib prolongs the lives of patients with multiple myeloma who are not candidates for high-dose chemotherapy.

Until recently, the therapeutic options for patients with multiple myeloma (MM) were limited to glucocorticosteroids and chemotherapy, either alone or in combination. Attempts to improve upon the outcome with more complicated regimens involving these types of drugs were more toxic and did not improve efficacy for elderly patients.[1] Preclinical studies showed that several new agents for the treatment of MM, including the proteasome inhibitor bortezomib, and the immunomodulatory agents thalidomide and lenalidomide, not only demonstrated anti-MM activity as single agents but also enhanced the efficacy of both chemotherapy and steroids. Interestingly, these new agents have novel mechanisms of action, which include an ability to enhance the anti-MM effects of both chemotherapy and steroids in the laboratory.[2] Single-arm studies have suggested that combinations of these new agents and chemotherapy and steroids were more effective than either the old regimens or the new agents alone.[3] Clinical trials were undertaken and results suggested that the addition of bortezomib to chemotherapy led to higher response rates than reported previously with either drug class alone.[4] A large, multicentre, randomised trial compared the 'gold standard' treatment, oral melphalan and prednisone, with or without bortezomib, for newly diagnosed patients who were not candidates for high-dose therapy. The study by San Miguel and colleagues confirms, for the first time, that the addition of bortezomib improves not only response rates but also overall survival for such patients.[4] This study changes the paradigm for the treatment of myeloma, and has opened the door to many new therapeutic approaches that combine the 'old' and 'new' classes of drugs. This randomised phase III trial enrolled 682 previously untreated patients with MM who were not candidates for high-dose therapy. Patients were randomly allocated to oral melphalan and prednisone with or without the addition of bortezomib for a maximum of nine six-week cycles. The

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primary endpoint of the trial was the time to disease progression, and secondary endpoints included rate of complete response, the duration of response, the time to subsequent therapy and overall survival. The study demonstrated not only an improvement in time to disease progression but also a marked increase in complete response rate (33% vs 4%) and overall survival in favour of the bortezomib-containing arm.

Clinical studies have also evaluated bortezomib with other alkylating agents, such as cyclophosphamide and prednisone, with promising results.[5] In addition, studies are beginning with bortezomib and another alkylating agent, bendamustine.[6] Anthracyclines show excellent activity when combined with bortezomib, with improved survival compared with bortezomib alone in the relapsed or refractory setting (P=0.0476).[7] Thalidomide has also shown excellent results when combined with melphalan and prednisone.[8]

Of particular interest is the ability to use classes of drugs with differing toxicities together in an attempt to give patients drug combinations that are not only more effective but also better tolerated. Examples include the combination of bortezomib with chemotherapeutic agents such as melphalan or pegylated liposomal doxorubicin.

As a result of the demonstration of marked synergistic anti-MM effects with these combinations in the laboratory,[2] low-dose treatment strategies are being studied in the clinic – with excellent anti-MM activity, reduced adverse effects and better-tolerated regimens.[3] Immunomodulatory agents are also being used in combination with bortezomib and chemotherapy and steroids in many clinical trials, with early reports of high levels of activity. It will be important to establish that these more complex and toxic combination therapies not only achieve higher response rates but improve survival as well.

In addition, with the ever-increasing choices available, the development of ways to select therapies for individual patients on the basis of both disease and patient characteristics must be addressed. Although several staging systems have been developed to predict outcome for patients with MM, the relevance of these systems, and other previously established prognostic factors, to patients receiving these new regimens has not been established. In fact, in the study by San Miguel et al, these prognostic factors did not prove to predict outcome for the patients randomly allocated to receive bortezomib.[4]

Clinicians must also keep in mind that, despite these advances, MM remains incurable at present and, as a result, patients are plagued by multiple recurrences. Thus, therapies that are overly aggressive with long-term toxicities could preclude future treatment options for these patients; high response rates that are only of brief duration, especially in the frontline setting, ultimately do these patients a disservice.

Besides enhancing the efficacy of chemotherapy, bortezomib also shows radiosensitising effects. On the one hand, this might increase the adverse effects of radiotherapy, making it difficult to use this drug for patients also receiving this treatment modality, especially when vital organs or the spinal cord could be affected by the radiotherapy. Alternatively, the delivery of radiotherapy specifically to the site of the tumour in the bone marrow might have enhanced efficacy with the addition of bortezomib. Preclinical studies demonstrate this effect of bortezomib when combined with the bone-seeking radionuclide samarium153 lexidronam on both human and mouse myeloma. A clinical trial using this combination to treat heavily pretreated patients with MM showed encouraging results with excellent tolerability.[9]

Other drugs with minimal activity as single agents for patients with MM, such as arsenic trioxide, also show chemosensitising and radiosensitising effects on MM cells in the laboratory, and have produced high response rates when combined with melphalan or thalidomide and steroids for previously heavily treated patients with MM.[10]

Although histone deacetylase inhibitors show little single-agent anti-MM activity in clinical studies, these drugs have shown chemosensitising effects in the laboratory, and early clinical results for previously treated patients with MM seem to show anti-MM effects when drugs from this new class are used in combination therapies.

The treatment options for patients with MM have increased in the past year, and it is likely that the study by San Miguel et al is only the beginning of a journey that will allow patients to live longer, and more fulfilled, lives with this incurable B-cell malignancy.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Practice point

Bortezomib enhances the anti-multiple-myeloma activity of standard chemotherapy, resulting in improved overall survival for patients with multiple myeloma who are not candidates for high-dose chemotherapy.

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