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Improving the treatment paradigm for non-Hodgkin's lymphoma with bortezomib

P.L. Zinzani

Institute of Hematology and Oncology "Seràgnoli" University of Bologna, Italy

Targeting of the ubiquitin proteasome pathway has proven to be a valid and efficacious approach for the treatment of several hematologic malignancies, especially multiple myeloma and select non-Hodgkin's lymphoma (NHL) subtypes. To date, several ongoing phase II clinical studies have independently and clearly documented the activity of bortezomib in select sub-types of NHL. What has emerged from the available data is that there may be significant differences among the different sub-types of lymphoma with regard to their sensitivity of proteasome inhibition and the kinetics of the response.

For example, in a multicenter study conducted from Memorial Sloan-Kettering Cancer Center (MSKCC), 65 patients were registered to a single agent study of bortezomib in patients with indolent and mantle cell lymphoma (MCL). These include 35 patients with MCL, 19 with follicular lymphoma (FL), six with marginal zone lymphoma (MZL) and five with small lymphocytic lymphoma/chronic lymphocytic leukemia (CLL). The population demographics included a median age of 66 (43 to 84), 42 males and 23 females. The median number of prior conventional chemotherapies for the population was three, and when individual courses of rituximab were considered, the median number was four. Overall, the population was heavily treated with alkylator-based treatment programs, and included patient status post-peripheral blood stem cell transplants and radioimmunotherapy, none of whom appeared to exhibit increased toxicity over other patients. All but one patient had received some form of treatment prior to receiving bortezomib. All patients were treated at a dose of 1.5 mg/m^2 twice weekly for two consecutive weeks with a one week rest period.

The only grade 3 or greater toxicities seen were lymphopenia (40% of patients) in patients that developed a grade 3 sensory and motor neuropathy. Re-staging studies were routinely performed after two complete cycles of therapy. The overall response rate was 52%. Of the evaluable patients, the overall response rate (ORR) in FL and MCL was 60% (one complete response (CR)/one complete response unconfirmed (CR)) and 54% (three CR, two CRu) respectively. Interestingly, 34% of patients with MCL had stable disease on study despite progression of disease at study entry. The time to response (TTR) was also different between these two populations, with a median TTR of five weeks and eleven weeks in patients with MCL and FL, respectively. The progression free survival (PFS) among all patients with MCL versus alt other NHL was seven months and five months, respectively. However, among all responding patients on study the PFS was 18 months. When broken down by subtype, the PFS among responding patients with MCL and FL was one year (range six months to 19 months) and 18 months, respectively. Comparison to the PFS obtained from the line of treatment prior to drug administration was uniformly better for patients receiving bortezomib. This study continues to accrue patients with different sub-types of NHL, and continues its follow-up of all patients treated on study.

Corroborating results have also been presented by Goy *et al.* who originally stratified patient populations according to MCL versus all other sub-types of lymphoma. These data, while demonstrating marginal activity in diffuse large B-cell-lymphoma, have confirmed significant single agent activity in MCL, with an overall response rate in this population of 41%, including six CR and six partial response (PR), with a median duration of response of six months. Similarly, data from Strauss and Lister have shown that using a dose of 1.3 mg/m^2 on the same day one, four, eight and eleven schedule that of 18 evaluable patients with MCL there was an overall response rate of 39% that included one CR and six PR. They also noted responses

in follicular lymphoma that occurred late, similar to what has been reported by the MSKCC group.

Collectively, these and other studies have confirmed significant activity of bortezomib in patients with various sub-types of NHL. Future studies will be devoted to understanding the duration of these responses, the biological basis for response in different sub-types of disease, and how best to integrate bortezomib into the standard conventional treatment paradigms for the treatment of NHL.