HEMATOLOGY

Bortezomib enhances chemotherapy effects in ABC DLBCL

A study has shown that bortezomib can enhance the activity of doxorubicin-based chemotherapy for the treatment of activated B-cell-like (ABC) diffuse large B-cell lymphoma (DLBCL). This hematologic malignancy has a particularly poor prognosis and is the DLBCL subtype least curable with current chemotherapy regimens. “By observing that the ABC subtype had a significantly improved outcome, we have provided the first clinical evidence that bortezomib may enhance the activity of chemotherapy in the ABC subtype,” comment the researchers.

The molecular classification of DLBCL by gene-expression analysis has revealed several subtypes of this tumor. The germinal center B-cell-like (GCB) and ABC subtypes arise from different cellular origins, and genetic analysis has confirmed that these two subtypes are pathogenetically distinct diseases. In most cases of ABC DLBCL, the NF- κ B pathway is constitutively active, and 10% of these tumors have somatic mutations in the *CARD11* gene, which encodes a scaffolding protein involved in the NF- κ B pathway. Studies have shown that when treated with doxorubicin-based chemotherapy patients with the ABC subtype of DLBCL have a considerably worse survival compared with the GCB subtype.

The researchers hypothesized that since NF- κ B is activated in ABC DLBCL, inhibition of this target might sensitize ABC to chemotherapy and thereby improve the outcome of patients with this subtype compared with GCB. Therefore, the investigators assessed whether addition of bortezomib—which is known to target the NF- κ B pathway—to doxorubicin-based chemotherapy could preferentially improve the survival of patients with the ABC compared with the GCB DLBCL subtype.

In total, 49 patients with relapsed or refractory DLBCL were enrolled in this multicenter study. The study was divided into two parts: in part A 23 patients received bortezomib alone and in part B 44 patients received the combination of bortezomib and dose adjusted

H&E staining of a DLBCL showing CD10 negative (middle panel) and MUM1 positive (lower panel) staining. Courtesy of K. Dunleavy, NIH, Bethesda, MD.

doxorubicin-based chemotherapy (DA-EPOCH) if their disease was deemed too advanced to warrant treatment with single-agent bortezomib. The activity and maximum tolerated dose of bortezomib were assessed, and the efficacy and toxicity profile of the bortezomib and DA-EPOCH regimen was also analyzed. As it was not possible to include a randomized design in this study owing to the small numbers of patients, and because there were no data on the outcomes of patients with ABC or GCB DLBCL, the researchers performed a survival analysis of a separate cohort of patients who progressed after standard

rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, according to their molecular subtype. This analysis required a superior outcome for patients with the ABC rather than GCB subtype in response to bortezomib treatment.

The survival times were equally poor in patients who received upfront chemotherapy regardless of whether they had ABC or GCB DLBCL. Among the 23 patients in the first part of the study, one patient had a partial response, and of the 44 patients in the second part of study, 15 responded, of whom eight had a complete response. In patients who received bortezomib and DA-EPOCH chemotherapy, there was a significant difference in the response rates for the two subtypes, with 13% of patients with GCB responding compared with 83% of patients with the ABC subtype. Notably, 41.5% of patients with the ABC subtype achieved complete remission compared with only 6.5% with GCB. When responses were analyzed based on classification by gene-expression profiling or immunohistochemistry, both techniques showed similar results in terms of identifying differences in overall response between the two molecular DLBCL subtypes.

Analysis of overall survival showed a significant difference between patients with GCB and ABC, with 3.4 and 10.8 months, respectively. “Our study provides provocative evidence for the utility of bortezomib in combination with chemotherapy for the treatment of ABC DLBCL,” the researchers conclude. The authors comment that their results provide the justification for a randomized comparison of rituximab-CHOP with and without bortezomib in untreated patients with ABC DLBCL.

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Original article Dunleavy, K. *et al.* Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. *Blood* **113**, 6069–6076 (2009).