1647 Safety, Tolerability and Activity of Ofatumumab, Bendamustine and Dexamethasone Combination As First-Line Treatment of Mantle-Cell Lymphoma in the Elderly: A Multicenter Study

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Background and Aims

Mantle cell lymphoma (MCL) is the aggressive subtype of non Hodgkin's lymphoma with the poorest long-term survival probability. There is no consensus for its treatment: in most cases, R-CHOP immuno-chemotherapy, with its 34% complete remission (CR) rate, is still considered the standard of care. Very encouraging results have been reported using more aggressive induction treatments as first-line therapy but these have a role only in the initial management of clinically fit patients less than 60-65 years of age. Since the median age at diagnosis is 63 years and intensive treatment tend to be poorly tolerated by elderly patients, a frontline therapy that can be administered to this category of patients is needed. The main objective of the present study was to design a well tolerated regimen, applicable to the vast majority of patients over 60 years with MCL, while improving the limited efficacy of R-CHOP immunochemotherapy. To achieve this goal, we have used two novel drugs, i.e. ofatumumab and

bendamustine. Ofatumumab is a fully human monoclonal antibody targeting a unique epitope on the CD20 molecule: its superior complement-dependent cytotoxicity compared to rituximab may translate into longer duration of treatment response. Bendamustine is a unique agent with both nitrogen mustard group and a benzimidazole ring: when given to relapsed or refractory MCL patients in combination with rituximab, it has shown a very favourable toxicity profile, as well as considerable activity.

Methods

Previously untreated patients with MCL, any stage (patients with disease limited only to the bone marrow were excluded), aged ≥ 60 years, were enrolled into a therapeutic protocol consisting of six cycles of immunochemotherapy as follows: ofatumumab 1000 mg i.v. on day 1 (300 mg only for the first cycle); bendamustine 120 mg/sm i.v. on day 2 and 3; dexamethasone 40 mg i.v. on day 1 to 4. Each cycle of therapy was administered every 21 days. Hematopoietic growth factors were used in case of neutropenia.

Results

As of July 31, 2011, 36 of the 50 planned patients have been enrolled and 19 have received the whole treatment. Cyclin D1 immunohistochemistry was positive in 18 patients (95%), thus confirming the diagnosis, while in the patient found negative at cyclin D1 analysis, Sox11 was used to confirm MCL; 1 patient (5%) had blastoid histology. Median age was 69 years (range 60-81), stage at diagnosis was IV in 95% of patients; MIPI score was low in 8 (42%), intermediate in 8 (42%) and high in 3 patients (16%); there were 15 male (79%) and 4 female patients (21%). Bone marrow (BM) involvement was detected by immunohistochemistry in 15 (79%) patients and by polymerase chain reaction (PCR) in all patients. Involvement of peripheral blood was detected by flow-cytometry in 12 cases (63%), by PCR in 18 cases (94%), while no data were available in the remaining case. A molecular probe was available for all patients: bcl1/IGH rearrangement was detected by PCR in 11 patients (58%), and an IGH allele-specific oriented primer was designed for the remaining 8 patients (42%).

Most adverse events (AEs) were mild or moderate in severity. The most common grade ≥ 3 treatment-related AE were neutropenia (10.5%), febrile neutropenia (10.5%), anemia (5.2%) and thrombocytopenia (5.2%). Two patients (10.5%) experienced tumor lysis syndrome: one was complicated by acute renal failure and the other by disseminated intravascular coagulation; both recovered with adequate therapy. Infectious complications consisted of one episode of pneumonia and one herpes zoster reactivation: both cases were resolved with antibiotic and antiviral therapy, respectively. Of note, 10 patients (52%) experienced cytomegalovirus reactivation, detected as pp65 antigen immunofluorescence, without evidence of infection: all these patients received anti-CMV therapy with negativization of the assay.

Among the 19 patients evaluable for response, overall response rate was 94%, with CR in 17 patients, partial remission in one patient and progressive disease after the second cycle in one patient; 15 out of 15 patients evaluable for minimal residual disease in the BM showed molecular remission.

Conclusions

Chemotherapy with bendamustine and ofatumumab appears generally safe and well tolerated to date in MCL patients aged ≥ 65 years requiring treatment. Preliminary data about efficacy are encouraging: accrual is ongoing for further evaluation.

Disclosures: Off Label Use: ofatumumab, in label for CLL.

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