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Monoclonal antibodies (novel): humax-CD20, ofatumumab

Ofatumumab, the first fully human anti-CD20 monoclonal antibody, targets a novel epitope of the CD20 molecule on B-cells and releases only very slowly from the target compared with rituximab. The antibody is generated via transgenic mouse and hybridoma technology. Compared with rituximab, ofatumumab has similar ADCC, but stronger CDC, even to lymphoma cells with a low CD20 antigen density and a high number of CD55 and CD59 complement inhibitory molecules present in the cell membrane. In addition, ofatumumab kills fresh B-CLL cells resistant to rituximab. In the cynomolgus monkey model, the ofatumumab-depletion of B-cells from peripheral blood and lymph nodes lasted longer than the depletion induced by rituximab.

Given the above, ofatumumab has the potential to treat B-cell malignancies with low CD20 expression, such as B-CLL and rituximab-refractory follicular lymphoma.

Indeed, in a multicenter dose-escalating study including 33 patients with relapsed or refractory CLL (Binet stage B: 67%; median number of previous treatments: 3). The response rate in the cohort receiving the highest doses (first infusion 500 mg, followed by 3 infusions of 2000 mg each, given at weekly intervals), a response rate of 50% (13/26) was achieved (Coiffier *et al.*, 2008). No complete remissions were observed. Most patients showed more than 50% decrease in lymph node size from week 4, which was sustained until week 15. The median percentage reduction from baseline of malignant $CD5^+$ $CD19^+$ B-cells in the peripheral blood was 97%, which lasted until week 24. Infections were experienced by 17/33 patients (51%), 88% of these were of grade 1/2. One event of interstitial pneumonia was fatal.

In relapsed/refractory follicular lymphoma, 4 dose groups of 10 patients each received 4 weekly infusions of 300, 500, 700 or 1000 mg. Patients had a median of 2 prior FL therapies. No safety concerns or maximum tolerated dose were identified. Treatment caused immediate and profound B-cell depletion lasting up to 1 year and 65% of patients reverted to a negative bcl2 status. Clinical response rates range from 20-63%, without a clear-cut dose-response relationship. Median time to progression for all patients/responders was 8.8/32.6 months and median duration of response was 29.9 months (Hagenbeek *et al*., 2008).

Based on these promising data, several new ofatumumab trials were launched, e.g. in CLL addressing the efficacy in patients

failing ≥1 Fludarabine- or Alemtuzumab-containing regimen and in follicular lymphoma addressing the response rate and response duration after ofatumumab treatment in patients refractory to rituximab.

References

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