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Current status and future perspectives

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The success of radioimmunotherapy (RIT) in lymphoma can be attributed to the combination of radio-sensitivity of the disease, the targeting of highly expressed antigens by signaling antibodies or by antibodies that mediate other therapeutic effects in their own right.

Two radiolabelled anti-CD20 antibodies are mostly used in clinic, i.e. 90Y-ibritumomab tiuxetan, Zevalin® (IDEC Pharmaceuticals and Schering AG) and 131I-tositumomab, Bexxar® (Glaxo Smith Kline). They are both approved for the treatment of /relapsed or refractory follicular/low-grade or transformed B-cell lymphoma including rituximab-refractory follicular B-cell lymphoma in the US but only Zevalin has been approved in the EU and only for follicular lymphoma. Both are more efficacious at inducing remissions compared to the respective naked antibody (including rituximab) and also more effective than prior course of therapy in these patients. Clinically, as a single modality, RIT can induce a high percentage of remissions, some of which are of impressive duration, in indolent and transformed B-cell lymphoma.

A single course of 131I-tositumomab as frontline therapy (1) can induce 75% complete remission (CR) in patients with advanced follicular lymphoma. The authors found that 81 % of the patients who had both a CR and molecular response with regard to BCL2 gene, had a progression-free survival of 5 years, suggesting for this very favorable subset of patients (i.e. initial therapy of follicular B-cell lymphoma) may not benefit from additional or more intensive treatment.

Morschhauser et al (2) have recently demonstrated in a randomised fashion that consolidation therapy with 90Y-ibritumomab tiuxetan after induction chemotherapy markedly prolongs progression-free survival in patients with previously untreated stage III or IV follicular lymphoma and prompted the approval of this agent for frontline consolidation therapy.

Attempts to optimise the efficacy of radioimmunotherapy of B-cell lymphoma are ongoing for refractory/relapsed indolent and aggressive B-cell lymphomas. Three factors need to be considered: choice of antibody/antigen, choice of radionuclide, choice of delivery system /schedule. A development is to explore the concept that agents targeting two different antigens on tumor cells, which may at least in part have different mechanisms of action, might have additive or synergistic anti-lymphoma effects or could potentially overcome single-agent resistance. A combination of epratuzumab (anti-CD22) with rituximab (anti-CD20) has shown to be well tolerated and having a significant clinical activity in aggressive and indolent B-cell lymphoma (3). By using rituximab there is a risk of blocking CD20 target for the subsequent RIT. This might be circumvented by target with an alternative B-cell surface with RIT, such as CD19, CD22 or CD45. A further development to explore would be to combine different antibodies labelled with different radionuclides. Beta-emitting radionuclides (i.e. 90Y, 131I, 67 Cu, 177Lu) are mostly used for B-cell lymphomas in clinical trials. In the treatment of microscopic disease and leukemia these radionuclides are not very feasible due to their high energy results in energy deposition beyond the targeted cell. Another option is then the use of targeted alpha particles. Radioimmunotherapy (RIT) is limited by the absorbed dose to radiosensitive organs, viz. bone marrow, lung, liver, and kidney. The bone marrow is the first dose-limiting organ in "high-dose RIT", but myeloablation can be circumvented by stem cell support (4; 5). To avoid toxicity of the other radiosensitive organs, other strategies must be used as pretargeting (6) or affinity-adsorption procedures (7).

References

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