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EDITORIAL

Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma: moving targets

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In 1997 rituximab, a chimeric monoclonal anti-CD20 antibody, was the first monoclonal antibody to be approved by the US Food and Drug Administration (FDA), based on the results of a rather limited phase II trial in 166 patients with relapsed/refractory follicular lymphoma. In the last decade the impressive results of a substantial number of randomised clinical trials have totally changed treatment paradigms in B-cell non-Hodgkin's lymphomas. Importantly, its widespread use and associated commercial success have also given an enormous boost to the development of other monoclonal antibodies.

As of 2009, the combination of rituximab and chemotherapy (R-Chemo) is the standard of care for remission induction treatment for both follicular lymphoma and diffuse large B-cell lymphoma because it results in a significantly better progression-free and overall survival than chemotherapy alone.[2-5] In relapsed follicular lymphoma, this should be followed by rituximab maintenance treatment.[6] However, resistance develops in about 50% of previously sensitive patients. Possible mechanisms of rituximab resistance are shown in *table 1*. Two interesting papers address novel treatment options for rituximab-resistant patients.[7,8] In the July/August issue of the *Netherlands Journal of Medicine*, Meerten and Hagenbeek discuss the second- and third-generation anti-CD20 antibodies. These antibodies differ from rituximab in their capacity to differentially activate the three possible effector mechanisms of monoclonal antibodies: antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and direct induction of apoptosis. The key question of course is whether these antibodies are effective in patients not or no longer responding to rituximab. If so, they offer an important expansion of our salvage treatment options. The data from the first clinical trials addressing this issue are promising, notably for ofatumumab (a fully human anti-CD20 antibody with strong complement-activating properties) and GA-101 (a humanised anti-CD20 antibody, engineered to improve direct apoptosis induction and antibody-dependent cellular cytotoxicity). Furthermore these antibodies might be superior to rituximab in non-resistant patients. Obviously this should be demonstrated by head-to-head comparison in randomised phase III trials.

In this issue, Czuczman and Bhat discuss the state of the art as to novel monoclonal antibodies against antigens other than CD20. The list is already quite impressive with 17 antibodies, two of which are directed against T-cell specific antigens (CD2, CD4). From their overview it is clear that the data are still rather limited with the exception of the anti-CD52 monoclonal antibody alemtuzumab. However, thus far the results obtained in the phase I/II trials using these novel antibodies as monotherapy appear to be less impressive than those with the anti-CD20 antibodies. Thus, the logical next step will

Table 1. *Possible mechanisms of rituximab resistance*

	Primary mechanism	Consequence
Tumour related	• Loss of CD20 expression	• No binding of antibody
	• Increased expression of complement inactivating molecules (e.g. CD55 and CD 59)	• Decreased complement dependent cytotoxicity
	• Intrinsic apoptosis resistance (molecular mechanisms largely unknown)	• No antibody-induced direct apoptosis
Host related	IgG Fc-gamma-receptor IIIA polymorphism	Decreased antibody-dependent cytotoxicity

be to study their capacity to improve the treatment results in combination with chemotherapy. Importantly, most of these antibodies have the same favourable toxicity profile as known from rituximab.

Another interesting option is the use of radiolabelled monoclonal antibodies, often referred to as the 'magic bullets'. At present two of these, both targeting CD20, have been approved for relapsed or refractory follicular lymphoma. A theoretical advantage of radiolabelled antibodies is the phenomenon of cross-fire, i.e. their capacity to kill CD20-low or -negative lymphoma cells (insensitive to non-radiolabelled antibodies) in close proximity to the CD20-positive lymphoma to which the radiolabelled antibody has bound. In Europe only the yttrium-90 labelled ibritumomab tiuxetan (Zevalin®) is available. In a direct comparison, this antibody proved to be more effective than rituximab monotherapy in patients with relapsed or refractory follicular or transformed lymphoma.[9] In addition, they show efficacy in rituximab-resistant follicular lymphoma patients.[10] Its role in diffuse large B-cell lymphoma is still under investigation. A recent randomised study showed that, when used after frontline chemotherapy, ibritumomab tiuxetan improved the complete remission rate and progression-free survival in patients with follicular lymphoma.[11] It remains to be seen whether similar results can be obtained in patients treated with the R-chemo remission induction treatment that is now standard.

Both papers make it very clear that the field of immunotherapy of non-Hodgkin's lymphoma is really booming and that rituximab has been the fascinating start but that it certainly will not be the end.[12]

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