Can radioimmunotherapy promote from an orphan drug to daily clinical practice?

Felix M. Mottaghy

Published online: 6 March 2014
© Springer-Verlag Berlin Heidelberg 2014

The concept of using radiolabelled antibodies to deliver radiation specifically to cells expressing specific antigens has a longstanding history in preclinical nuclear medicine research [1–3]. Several approaches were used as long ago as some 50 years to evaluate the potential therapeutic effect in different xenograft models [2, 3]. Promising results were shown in different tumour cell lines in vitro and in vivo [4–7]. One of the first human applications was reported in the late 1960s [8]. All these studies have in common that they used heterologous antibodies generated in different species and mostly labelled with ^{131}I . Due to the large size of complete antibodies they display a less favourable biodistribution pattern. One of the important aspects is a rather long blood-pool half-life which leads to an increased risk of deiodination and thereby the risk of an increased dose to the thyroid and at the same time lower accumulation in the targeted tumour. Other radionuclides such as ^{90}Y [9], ^{177}Lu [10] or different alpha-emitters (see for example Chen et al. [11]) might be more effective due to a expected higher linear energy transfer and a higher stability in vivo. Furthermore, complete antibodies are more easily recognized by FcR-expressing cells such as macrophages and granulocytes. Another point is the expected diminished capacity for penetration into tumours due to the size of the antibodies.

In haematological malignancies, two monoclonal antibodies against the surface antigen CD20, overexpressed in B-cell lymphomas, have made their way into registration and thereby clinical application outside study protocols [12]. In

solid tumours several phase I and II studies have been performed, but a registered product is not yet available (see for example Stillebroer et al. [10]).

It is intriguing that as early as almost 30 years ago a study evaluated a promising approach in refractory Hodgkin lymphoma using a ^{131}I -labelled antiferritin antibody showing a symptomatic response rate of almost 80 % [13]. Several studies followed with the same polyclonal antibody, some of them using ^{90}Y as the radionuclide, with comparable results [14]. Despite these seemingly good results only a few further studies followed, the last one in 2007 in ten patients [15]. In a phase I study another approach, a chimeric antibody to the alpha chain of the interleukin-2 receptor (CD25), was evaluated with promising results [16], but no further studies have been published. One of the problems of the concepts was most likely the nonhumanized antibodies and/or the use of a polyclonal antibody. But in the author's opinion, the broad underlying problem – not only concerning new radiolabelled therapeutic agents but in general a lot of promising new molecular probes for theranostic applications – lies most likely in the lack of economic power behind these concepts. Within academia phase 0 and I, and perhaps even phase II, studies can be financed, but at the point of registration and potential translation to general clinical application big pharma companies should come into the field, and that in a lot of cases is simply not happening. The current options for European grants within the new Horizon 2020 programme [17] might give the opportunity to establish consortia for the realization of larger multicentre trials.

Regarding the biodistribution of the complete antibodies so far evaluated in most studies, developments in the engineering of antibodies and antibody fragments might provide a completely new opportunity for theranostic concepts using specific extracellular or cellular surface targets in personalized medicine and could potentially further accelerate the concept of delivering radioactivity directly to the target [18]. The

F. M. Mottaghy
Department of Nuclear Medicine, University Hospital RWTH Aachen University, Pauwelsstr. 30, 52057 Aachen, Germany

F. M. Mottaghy (✉)
Department of Nuclear Medicine, Maastricht University Hospital MUMC+, P. Debyeilaan 25, 6229, HX Maastricht, The Netherlands
e-mail: fmottaghy@ukaachen.de

potential role played by nanotheranostics in this context should also be mentioned.

In the current issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Luigi et al. [19] present the results of a phase I/II study in eight patients with therapy-refractory Hodgkin lymphoma using a radiolabelled miniantibody against the extracellular matrix (ECM) domain molecule tenascin-C (TC-A1). In a previous study other tumour entities were also treated with a comparable radiopharmaceutical [20]. Tenascin-C plays a role in the mechanical and signalling function of the ECM in inflammatory processes (especially chronic inflammation) as well as in cancerogenesis and is therefore a potentially interesting target for a variety of malignancies [21]. Moreover, tenascin-C is involved in angiogenesis and its expression has been shown to correlate with the degree of vascularization of the tumour. Especially in malignant lymphoma, tenascin-C expression is correlated with a poor prognosis [21]. These features support the statement that the new miniantibody TC-A1 (Tenarad) has the potential to become an important radioimmunopharmaceutical in several tumour entities either as a first-line therapy or in combination with standard chemotherapies. In general radioimmunodiagnosis and radioimmunotherapy, together radioimmunotheranostics, are siblings with a bright future if enough economic and scientific power is made available for their further evolution.

References

1. Bale WF, Spar IL. In vivo localization of rat organ antibodies in ovaries, adrenals, and other tissues. *J Immunol*. 1954;73:125–33.
2. Bale WF, Spar IL, Goodland RL. Experimental radiation therapy of tumors with I-131-carrying antibodies to fibrin. *Cancer Res*. 1960;20:1488–94.
3. Bale WF, Spar IL. Studies directed toward the use of antibodies as carriers of radioactivity for therapy. *Adv Biol Med Phys*. 1957;5:285–356.
4. Goldenberg DM, Gaffar SA, Bennett SJ, Beach JL. Experimental radioimmunotherapy of a xenografted human colonic tumor (GW-39) producing carcinoembryonic antigen. *Cancer Res*. 1981;41:4354–60.
5. Ghose T, Norvell ST, Aquino J, Belitsky P, Tai J, Guclu A, et al. Localization of 131I-labeled antibodies in human renal cell carcinomas and in a mouse hepatoma and correlation with tumor detection by photoscanning. *Cancer Res*. 1980;40:3018–31.
6. Ghose T, Tai J, Guclu A, Norvell ST, Bodurha A, Aquino J, et al. Antibodies as carriers of radionuclides and cytotoxic drugs in the treatment and diagnosis of cancer. *Ann N Y Acad Sci*. 1976;277:671–89.
7. Ghose T, Guclu A, Tai J, MacDonald AS, Norvell ST, Aquino J. Antibody as carrier of 131I in cancer diagnosis and treatment. *Cancer*. 1975;36:1646–57.
8. Spar IL, Bale WF, Marrack D, Dewey WC, McCardle RJ, Harper PV. 131I-labeled antibodies to human fibrinogen. Diagnostic studies and therapeutic trials. *Cancer*. 1967;20:865–70.
9. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today (Barc)*. 2004;40:111–9.
10. Stillebroer AB, Boerman OC, Desar IM, Boers-Sonderen MJ, van Herpen CM, Langenhuijsen JF, et al. Phase I radioimmunotherapy study with lutetium 177-labeled anti-carbonic anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma. *Eur Urol*. 2013;64:478–85. doi:10.1016/j.eururo.2012.08.024.
11. Chen Y, Kornblit B, Hamlin DK, Sale GE, Santos EB, Wilbur DS, et al. Durable donor engraftment after radioimmunotherapy using alpha-emitter astatine-211-labeled anti-CD45 antibody for conditioning in allogeneic hematopoietic cell transplantation. *Blood*. 2012;119:1130–8. doi:10.1182/blood-2011-09-380436.
12. Press OW. Radiolabeled antibody therapy of B-cell lymphomas. *Semin Oncol*. 1999;26:58–65.
13. Lenhard Jr RE, Order SE, Spunberg JJ, Asbell SO, Leibel SA. Isotopic immunoglobulin: a new systemic therapy for advanced Hodgkin's disease. *J Clin Oncol*. 1985;3:1296–300.
14. Vriesendorp HM, Morton JD, Quadri SM. Review of five consecutive studies of radiolabeled immunoglobulin therapy in Hodgkin's disease. *Cancer Res*. 1995;55:5888s–92s.
15. Decaudin D, Levy R, Lokiec F, Morschhauser F, Djeridane M, Kadouche J, et al. Radioimmunotherapy of refractory or relapsed Hodgkin's lymphoma with 90Y-labelled antiferritin antibody. *Anticancer Drugs*. 2007;18:725–31. doi:10.1097/CAD.0b013e3280678042.
16. Dancey G, Violet J, Malaroda A, Green AJ, Sharma SK, Francis R, et al. A phase I clinical trial of CHT-25 a 131I-labeled chimeric anti-CD25 antibody showing efficacy in patients with refractory lymphoma. *Clin Cancer Res*. 2009;15:7701–10. doi:10.1158/1078-0432.CCR-09-1421.
17. European Commission. Horizon 2020: The EU Framework Programme for Research and Innovation. 2014. <http://ec.europa.eu/programmes/horizon2020/>.
18. Knowles SM, Wu AM. Advances in immuno-positron emission tomography: antibodies for molecular imaging in oncology. *J Clin Oncol*. 2012;30:3884–92. doi:10.1200/JCO.2012.42.4887.
19. Luigi A, D'Ambrosio L, Aurilio M, Morisco A, Frigen F, Caraco C, et al. Radioimmunotherapy with Tenarad, a 131I-labelled antibody fragment targeting the extra-domain A1 of tenascin-C, in patients with refractory Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging*. 2014. doi:10.1007/s00259-013-2658-6.
20. Tijink BM, Neri D, Leemans CR, Budde M, Dinkelborg LM, Stigter-van Walsum M, et al. Radioimmunotherapy of head and neck cancer xenografts using 131I-labeled antibody L19-SIP for selective targeting of tumor vasculature. *J Nucl Med*. 2006;47:1127–35.
21. Midwood KS, Orend G. The role of tenascin-C in tissue injury and tumorigenesis. *J Cell Commun Signal*. 2009;3:287–310. doi:10.1007/s12079-009-0075-1.