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EDITORIAL COMMENTARY

Pretargeted radioimmunotherapy: clinically more efficient than conventional radioimmunotherapy?

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The clinical efficacy of radioimmunotherapy (RIT) has been clearly documented in the consolidation situation, such as first-line treatment of indolent non-Hodgkin lymphoma after induction chemotherapy [1] or after salvage resection of liver metastases from colon carcinoma [2], when tumour targets have a small, preferably microscopic, size. Efficacy has been much less evident for large tumours, more than 1–2 cm in diameter, especially for radioresistant tumours that need a higher absorbed dose and consequently a higher injected activity to be killed. The level of this injected activity is limited by the haematological toxicity following irradiation of bone marrow by the radioimmunoconjugate. One way to solve this problem is to limit the duration of such irradiation by decoupling the injection of the immunoconjugate and that of the radioactive effector which, due to its small size, can distribute rapidly so that irradiation of normal tissues is limited. This is the principle of pretargeted RIT (PRIT) which has been under development for more than 20 years.

Two main approaches have been preclinically and clinically tested: one uses the interaction of avidin (or streptavidin) and biotin, and the other the interaction of bispecific antibody (BsMAb) and hapten. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, van Rij et al. [3] report on the second of these approaches. After two decades of multiple preclinical and clinical studies in several tumour types and using different antibodies and radionuclides, it is time to wonder whether PRIT is indeed better than conventional RIT in terms of toxicity and efficacy.

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Preclinical comparison

It is quite clear that in preclinical studies which compared RIT and PRIT in three different tumour types using the same antibodies, PRIT was unambiguously superior to RIT with higher efficacy and lower or equivalent haematological toxicity. In a mouse model of LS174T human colorectal cancer ^{131}I-RIT using intact IgG was compared to ^{131}I-PRIT using the same anticarcinoembryonic antigen (CEA) antibody [4]. For PRIT a BsMAb/hapten molar ratio of 2:1 was used with an injected activity of 111 MBq of ^{131}I as compared with 12 MBq for RIT. The maximum tumour uptake was lower with PRIT (8.5 % ID/g at 1 h) than with RIT (33 % ID/g at 2 days), but resulted in an equivalent tumour absorbed dose (102 Gy versus 95 Gy) and a lower blood absorbed dose (15 Gy versus 33 Gy). With PRIT, tumour growth delay was superior at 150 days as compared to 53 days with RIT with an equivalent haematological toxicity. Longer term monitoring of treated animals and post-mortem examination of tumours showed that with PRIT, 33 % of the animals were cured, compared to none with RIT [5].

Using the same anti-CEA antibody, a similar comparison study was performed in a mouse model of TT human medullary thyroid carcinoma (MTC) [6, 7]. For PRIT, the BsMAb/hapten molar ratio of 2:1 was the same as in the previous study and the injected activity was 92.5 MBq for both approaches. Tumour growth delay was 86 days with PRIT as compared to 65 days with RIT, with a substantially higher haematological toxicity with RIT (89 % decrease in white blood cell count, 66 % decrease in platelet count) than with PRIT (34 % decrease in white blood cell count, 39 % decrease

in and platelet count). Recently, a new bispecific trivalent anti-CEA × anti-histamine-succinyl-glycine (HSG) antibody (TF2) was developed using Dock-and-Lock technology and used in the pretargeting of a bivalent HSG hapten referred to as IMP288 [8].

These new reagents allow the labelling of the di-HSG peptide with several radionuclides including ^{177}Lu. In a study performed in a mouse model of LS174T human colorectal cancer, mice treated with PRIT using an anti-CEA antibody with a BsMAb/hapten molar ratio of 18:1 and an injected activity of 26 MBq of ^{177}Lu showed a median survival of 45 days as compared to 13 days in untreated mice and a weak haematological toxicity [9]. In this study PRIT was not compared to RIT. Such a comparison has been performed by van Rij et al. [3]. In this study PRIT using the anti-TROP-2 TF12 and the ^{177}Lu-IMP288 peptide was compared with RIT in a mouse model of PC3 prostate cancer. For PRIT a higher molar ratio than in the initial studies (25:1 versus 2:1) was used with an equivalent injected activity for PRIT and RIT (13.7 MBq versus 11.1 MBq). The efficacy of PRIT was slightly inferior to that of RIT with a median survival of 90 days as compared to more than 120 days, but the haematological toxicity of PRIT was much lower. Using the same injected activity, a 81 % decrease in white blood cell count and a 61 % decrease in platelet count were observed with RIT as compared with no toxicity with PRIT. An optimization study of this novel Dock-and-Lock technology has been performed in a mouse model of LS174T human colon cancer [10]. As in previous studies, the maximum tumour uptake appeared lower with PRIT than with RIT but tumour-to-nontumour ratios and especially tumour-to-blood ratios were much higher. It was shown that high tumour absorbed doses could be obtained with short-lived radionuclides such as alpha particle-emitting ^{211}At, whereas repeated injections of long half-life beta-emitting radionuclides such as ^{177}Lu could be needed to get the same efficacy.

Clinical comparison

Clinical comparison of PRIT and RIT is much harder. Ideally this comparison should be done in a randomized trial using the maximum tolerated dose previously determined in phase I trials for each approach. In practice, such a comparison appears to be quite difficult if not impossible. Thus, the only way is to try to compare the efficacy and toxicity obtained in separate phases I/II trials using the same antibody and radionuclide. Such clinical studies have been performed in patients with metastatic MTC and colorectal carcinoma.

Medullary thyroid carcinoma

In one phase I/II trial and one phase II trial ^{131}I-PRIT was assessed in, respectively, 26 and 42 patients with advanced MTC [11, 12], and in one phase I/II trial ^{131}I-RIT using the anti-CEA MN-14 antibody was assessed in 15 patients with MTC [13]. The pretherapeutic calcitonin serum levels were equivalent in the two phase I/II studies (4,990 and 5,900pg/ml) suggesting roughly equivalent advanced disease. Injected activities for RIT varied from 3.7 GBq to 10 GBq (99 to 270 mCi) with 14 patients injected with more than 3.7 GBq (100 mCi) and for PRIT from 1.4 GBq to 4.1 GBq (38 to 112 mCi) with 4 patients injected with more than 3.7 GBq (100 mCi). Considering radiological and biological efficacy, stabilization was observed with RIT in 11 patients of 12 injected with a relatively high activity (>5.2 GBq or 140 mCi) and with PRIT in 6 patients of 17 including 3 of 4 injected with more than 3.7 GBq (100 mCi). Haematological toxicity was slightly higher with RIT (grade 3/4 in 47 % of patients) than with PRIT (grade 3/4 in 31 % of patients). Based on these results, we consider that it is not possible to conclude that PRIT is superior to RIT in terms of efficacy or toxicity. Bone marrow involvement has been reported in 76 % of patients with advanced MTC [14], and this could probably explain the high haematological toxicity, even with PRIT. The follow-up in patients in the PRIT study has been extended over a long period allowing the overall survival (OS) to be evaluated in comparison with that in 39 contemporaneous untreated patients with MTC with comparable prognostic indicators [15]. OS was significantly longer in the high-risk treated patients than in the high-risk untreated patients (median OS 110 and 61 months, respectively; $P<.030$). Unfortunately, this survival benefit of PRIT cannot be compared with that in the RIT study, in which the follow-up was much shorter. The phase II trial confirmed the efficacy of PRIT in progressive metastatic MTC, with a 76.2 % disease control rate [12].

Colorectal carcinoma

In patients with metastatic colorectal cancer two phase I/II trials have been performed with ^{131}I-RIT and ^{131}I-PRIT using MN-14 and F6 anti-CEA antibodies in, respectively, 17 and 8 patients [16, 17]. The pretherapeutic CEA serum levels were equivalent in the two studies (73 and 77 ng/ml) suggesting a roughly equivalent disease advancement. Injected activities with RIT varied from 2.1 GBq to 4.1 GBq (57.5 to 110 mCi) with four patients injected with more than 3.7 GBq (100 mCi) and with PRIT from 1.9 GBq to 5.5 GBq (51 to 149 mCi) with three patients injected with more than 3.7 GBq (100 mCi). No response was observed with RIT, whereas two patients injected with, respectively, 3 and 5.5 GBq had stabilization with PRIT. Interestingly, three of seven patients injected with more than 3.7 GBq had grade 4 haematological toxicity with RIT versus no patient with PRIT. These findings could mean that bone marrow involvement is less frequent in colorectal cancer than in MTC, and

that it may then be possible to inject a higher activity with PRIT.

Conclusion

Although PRIT appears clearly superior to RIT in all preclinical studies, it is not currently possible to claim that PRIT is clinically superior to RIT. However, the optimization of PRIT continues with Dock-and-Lock technology paying particular attention to the BsMAb/hapten molar ratio, which must be high to optimize tumour uptake (20:1 or higher). The specific activity of the radionuclide then becomes important. Radionuclides with a shorter half-life, such as ^{90}Y and ^{211}At, may prove more efficient than ^{131}I and the use of no carrier added ^{177}Lu, instead of conventional ^{177}Lu, is probably mandatory.

Regarding the most favourable clinical indication for documenting the potential advantage of PRIT, colorectal cancer could be relevant based on a previous phase II clinical study in which patients were injected with 2.2 GBq/m^2 of ^{131}I-labelled anti-CEA antibody. Only 1 of 28 patients had a grade 4 thrombocytopenia [18]. In the same clinical situation it would be interesting to check whether the optimized PRIT technique would allow the injected activity to be substantially increased for better efficacy without increasing haematological toxicity. Two phase I/II trials are ongoing in Europe using new-generation PRIT reagents in lung and colorectal carcinomas to optimize PRIT parameters.

In addition to therapeutic applications the pretargeting technique could be useful for immuno-PET applications. Imaging with intact antibodies requires a non-ideal delay of 4 to 7 days after injection before high-contrast images can be obtained. Imaging studies with smaller antibody fragments have demonstrated the possibility of obtaining images on the day of injection or the next day [19]. Pretargeting allows imaging within 1 h of injection of radiolabelled peptide with high contrast in animal models [20]. Two phase I/II trials are ongoing in France using new-generation pretargeted reagents in MTC and breast carcinomas to optimize pretargeted immuno-PET parameters.

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