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Radio-immunotargeting in Colorectal Carcinoma

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Colorectal cancer is one of the most frequently studied diseases for investigating cancer detection using radiolabelled monoclonal antibodies. From many clinical studies it has become clear that with radio-immunotargeting (RIT) it is possible to visualise approximately 70% of known sites of colorectal cancer and to find otherwise occult tumour deposits in approximately 10% of patients. The intra-operative use of a gamma detection probe increases the detection rate of clinical occult intra-abdominal tumour sites to 30–40%. However, this clinical experience has also disclosed the many difficulties and pitfalls connected with this technique, with respect to antibody-, tumour-, patient- and isotope-related factors. Upstaging or early disclosure of disseminated disease by RIT has not proven to be beneficial in terms of improved survival, but might be of use in the management of an individual patient. The laborious and costly RIT technique, difficult scan interpretation and the lack of proven survival benefit precludes its routine use in clinical practice. However, the promising results warrant further study to improve the technique, and to validate the clinical usefulness of radio-immunotargeting.

Key words: colorectal cancer, monoclonal antibodies, radio-immunotargeting, clinical value
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INTRODUCTION

THE CONCEPT of the "magic bullet" i.e. tumour targeting by specific tumour-seeking compounds in cancer patients has engaged scientists for almost a century. Since the availability of monoclonal antibodies (MAbs) raised against tumour-associated antigens following the conception of the hybridoma technique by Kohler and Milstein in 1975 [1] this dream appeared to become reality. Over the last decade, numerous studies have been published, describing the results of tumour targeting by radiolabelled MAb in cancer patients. Mach and colleagues [2] were the first to publish clinical results of the successful application of monoclonal antibodies (MAb) *in vivo*. Goldenberg and Larsson recently presented an excellent overview of the current status of radio-immunodetection in cancer identification [3].

In this review, the focus is on radio-immunotargeting (RIT) for diagnosis and staging in colorectal carcinoma. Questions concerning the clinical value will focus on patients with primary colorectal carcinoma, patients with "operable" relapse or with suspected relapse by a persistent carcino-embryonic antigen (CEA) rise without detectable disease. Immunotargeting for therapy will not be reviewed in this paper.

THE MONOCLONAL ANTIBODY AND LABEL

The most frequently used MAbs in colorectal carcinoma are B72.3, several anti-CEA antibodies and anti 17-1A antibodies [3]. The murine IgG antibody B72.3, developed by Colcher and associates, is reactive with a carbohydrate structure mainly present on the TAG-72 molecule [4]. This tumour-associated glycoprotein is a mucin. TAG-72 is expressed in most adenocarcinomas as ovarian, breast and colon. Another MAb directed against a different epitope in the TAG-72 antigen is CC49, which has a higher affinity [5]. *In vivo* applied anti-CEA antibodies are: ZCE-025 [6] and BW 431/26 [7, 8], both IgG antibodies binding with high affinity to cell-bound CEA protein epitopes. Mab 17-1A is directed against an antigen which is expressed only on colorectal carcinoma cell lines [9]. The majority of clinical RIT studies in colorectal carcinoma are performed with these MAbs.

As most MAbs generated today are of murine origin, one of the possible problems of their *in vivo* use is the formation of so called HAMA: human anti-mouse antibodies. HAMA formation might hamper secondary administration of murine MAb in patients because of the risk of sensitivity reactions, or very fast clearance of antigen–antibody complex. Furthermore, HAMA alters biodistribution [3]. Significant HAMA formation occurs in approximately 20–30% of patients [8, 10–13]. The degree of HAMA formation largely depends on the injected molecule: Fab hardly gives rise to HAMA formation, but after a single injection whole IgG more frequently results in HAMA. Whether HAMA formation precludes repeated imaging is, however, a matter of debate: RIT can be performed in HAMA positive patients, with no increase in adverse events [14]. Overall, side effects of low dose murine MAbs are extremely rare [6, 8, 13, 15–17]. In our experience of radio-immunotargeting in 140 patients with different types of cancer and with different MAbs, no strong allergic reaction or other adverse effects have been observed. However, in one case, unexpected brain uptake [18] was seen.

^{111}Indium, ^{99m}Technetium and ^{123}Iodine (^{123}I) are the most frequently used isotopes for RIT, all having their own advantages or disadvantages. However, because of its long half life and low energy, ^{125}I appears to be the most appropriate isotope for radio-immunoguided surgery [19]. For colorectal cancer, ^{111}Indium, which is retained in the liver, has limited value since it complicates the detection of liver metastases.

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PROBLEMS WITH *IN VIVO* USE OF MONOCLONAL ANTIBODIES

The most important problems and pitfalls of the *in vivo* use of MAbs are presented in Table 1. In our experience, these factors result in only a 0.01–0.001% of the injected dose of activity being found per gram of tumour tissue. In general, tumour to normal tissue ratio of radioactivity is only approximately 1:1.5–1:5. Some possible solutions for these problems have been studied *in vivo*. For example, by humanising the murine MAb, i.e. by replacing the constant domain of the murine IgG by human domains, HAMA formation can be largely prevented. Binding of MAb to circulating antigen or to non-specific ligands can be prevented by giving the patient an excess of cold antibody prior to the administration of the labelled antibody, with the intention of saturating non-specific binding sites and circulating antigen first. Another method of improving the targeting and diminishing background activity is the use of a bispecific MAb: one part of the specific region of the IgG molecule is directed against the tumour-associated antigen, the other part against a non-specific small molecule, for instance an oligopeptide, which is labelled with a radioactive isotope. An excess of this cold bispecific antibody is administered to the patient, and after a certain period, to allow clearance of circulating MAb, the labelled peptide is given. The peptide has the biopharmacokinetics of a small molecule and will quickly penetrate the tissues, binding to the specific region of the bispecific antibody; excess of this peptide with its radioactivity will be cleared from the circulation easily. These options, among many others, have to date not led to a major clinical improvement of radio-immunotargeting and have to be further refined for effective clinical use.

THE METHOD OF RADIO-IMMUNOSCINTIGRAPHY

The production and preparation of MAb for clinical use is a laborious and very costly process, which demands a highly qualified organisation. The MAb used *in vivo* must be pure, without DNA or pyrogen contamination and free of viruses, bacteria etc.

Provided one has the disposal of an approved MAb which is sufficiently immunoreactive after labelling with an isotope (at least 50% of the labelled product must be immunoreactive), usually 1–2 mg of labelled MAb will be administered i.v. to the patient. Depending on the presumed biopharmacokinetics of the antibody, planar images with the gamma camera will be taken at certain intervals: 6–24 h interval for Fab fragments, and 6–72 h interval for whole antibody. Three-dimensional display of the region of suspected tumour or regions, with only slightly increased activity by the so-called SPECT technique (single photo emission computerised tomography), may be an aid in the detection or localisation of tumours. Obviously, areas with unexpected increased uptake have to be investigated by other means (computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US)) or approached with special interest during surgery.

Table 1. *Problems and pitfalls with* in vivo *use of monoclonal antibodies*

A. MAb-related
Non-specific binding with normal tissue
Low affinity and binding capacity, depending on the choice of MAb
Fast clearance from circulation of small fragments
Poor stability of the protein–isotope linkage (e.g. rapid dehalogenisation)
HAMA formation
Biopharmacokinetics unpredictable
B. Patient-related
Tumour heterogeneity (not all cells have same expression of antigen)
Insufficient tumour vascularisation and necrosis
Antigen location (membrane, cytoplasmatic)
Shedding of the antigen
Circulating antigen

THE CLINICAL VALUE OF RADIO-IMMUNOTARGETING IN COLORECTAL CARCINOMA

Reviewing the literature on this subject, many problems have to be dealt with: all clinical studies have been performed retrospectively with a selected series of patients. Different MAbs have been used, with different labels, in different, usually small, patient groups. Data on particular patient groups, for example, patients with primary or recurrent colorectal carcinoma, are frequently not presented separately. The judgement "clinically valuable" is generally poorly described, and data on patient outcome and follow-up are never presented. These and other problems make the interpretation of the reported data on this subject very difficult. In our opinion, the clinical value of RIT has to be judged in three main patient groups.

1. Patients with primary colorectal carcinoma, with no clinical evidence of distant disease (excluded by traditional investigations: physical examination, chest X-ray, liver ultrasound or CT scan). Is RIT able to detect otherwise occult disease, which alters patient management to a clinically appreciable extent? From a clinical point of view, this will hardly ever be the case. Even patients with a newly diagnosed disseminated colorectal cancer usually undergo (palliative) surgery of the primary tumour to prevent serious sequelae, such as bowel obstruction, perforation or bleeding. Only if there is extensive dissemination will such a procedure be abandoned. However, this disease is clinically overt and usually does not require RIT for its detection. In the situation of extensive regional lymph node metastasis, for instance revealed pre-operatively by RIT, the value of subsequent, extensive, locoregional resection is still a matter of debate [20, 21]. Furthermore, it is unclear whether the early treatment of subclinical RIT detected distant colorectal metastasis results in survival benefit. Only complete surgical excision of isolated liver metastasis appears to have a positive impact on patient survival. However, these metastases can be detected during laparotomy clinically, or by intra-operative ultrasound [22]. In the situation of unexpected liver metastases found during laparotomy for resection of primary colorectal cancer, one can decide to remove the liver metastases immediately or in a delayed second procedure. Thus, from a clinical perspective, the value of RIT in primary colorectal carcinoma seems limited.

2. Patients with locoregional relapse or liver metastases of colorectal carcinoma, in whom surgical therapy is considered: in these patients, removal of the tumour following relapse is only worthwhile in the absence of other distant disease. For the detection or exclusion of other tumour locations, RIT, and particularly radio-immunoguided surgery (RIGS) [23] could be of use in these patients. Obviously, this demands a high sensitivity and specificity of the RIT method.

3. Patients with a persistent rise in serum CEA levels, detected during follow-up after curative treatment for colorectal carcinoma, without demonstrable disease by standard dissemination examination (chest X-ray, CT abdomen, liver ultrasound

and coloscopy): it may be possible to find the CEA-producing locus by RIT. However, will this result in the detection of "curable" disease in a substantial number of patients?

The clinical value of RIT, i.e. improvement in survival and quality of life, in the aforementioned patient categories, can only be judged in prospective randomised trials: one group diagnosed by standard means and treatment according to the clinical situation, versus treatment according to the RIT findings (more extensive surgery or refrain from surgery). Such a study is not ongoing and has never been performed. One should bear in mind that RIT is relatively expensive: the Dutch registered commercial available MAb B 72.3, including ^{111}Indium isotope, costs approximately U.S. $700 per investigation alone.

As stated above, it is difficult to establish the clinical value of RIT in colorectal cancer from published data. Some of the reported data on RIT in colorectal cancer are summarised in Tables 2–4. Table 2 shows results of this technique in a series of patients with predominantly operable primary colorectal cancer. In approximately 70–80% of cases, the already known tumour sites could be visualised. Only rarely were non-expected metastases found, usually in mesenteric and para-aortic lymph nodes. Maguire and associates [10] and Doerr and associates [11] stated that RIT findings, in approximately one-quarter of the patients, "significantly" influenced patient management, according to the judgement of the treating physician. However, data on to what extent this change in management affected the patient outcome was lacking.

In liver metastases, probably one of the major indications of performing RIT, there are important shortcomings. Frequently, metastases are depicted as "cold spots" (relatively low uptake of ^{111}Indium MAb) alternating with "hot spots". In the study by Abdel Nabi and associates [17], 9 patients had proven liver metastases: ^{111}In B 72.3 RIT showed 2 patients with hot spots, 4 with "cold spots" and 3 false negatives. Doerr and associates [11], using the same compound, had 3 patients with liver metastases, all false negatives. Furthermore, regularly false positive images are seen [16, 24].

Data on RIT in recurrent colorectal carcinoma are presented in Table 3. In these 4 studies, RIT was able to visualise usually known tumour deposits in 60–70% of cases, and again it was not possible to gather reliable information on the usefulness of RIT in clinical patient management. The experiences of Hölting and associates [24] with a ^{131}I-labelled anti-CEA MAb were discouraging, with a high number of false negative as well as false positive cases.

In patients with a CEA rise during follow-up, without detectable disease by conventional means, RIT is able to detect recurrences of colorectal carcinoma in a substantial number of patients (Table 4). However, in these rather small series of patients, only a few patients with operable (curable ?) disease could be found: generally, diffuse, multiple dissemination was seen for which no effective treatment is available.

Pelvic recurrences of rectal carcinomas are difficult to diagnose, particularly in patients who have had radiotherapy. CT scanning is not very reliable in distinguishing scar tissue from tumour. Possibly in these cases, RIT could be of use [16], particularly if the SPECT-method is used. However, the value of MRI or PET scanning (positron emission tomography) has to be established in this situation and be compared with RIT [25].

Comparing CT scanning with RIT: CT appears to be far more helpful in examining the liver [16, 26], but equivocal in detecting abdominal lymph node metastases or peritoneal metastases, whereas RIT might be more useful in the diagnosis of pelvic recurrences [11].

The interpretation of RIT images is not easy, as shown by the study of Davidson and associates [26]. They performed RIT in 22 patients with colorectal cancer using ^{111}In-labelled anti-epithelial membrane antigen MAb: the sensitivity (true positive rate) was reduced from 80%, when the reporting was unblinded, to 20% in blinded reporting (the nuclear physician was not aware of the disease status of the patient).

The group of Martin and colleagues [5, 27, 28] developed the concept of RIGS (radio-immunoguided surgery): after administration of ^{125}I-labelled whole MAb (B72.3, 17.1 A) and a waiting period of approximately 3 weeks to clear blood pool background activity, patients with recurrent colorectal cancer were operated on, and during surgery, the abdomen was scanned by a hand-held gamma ray detection probe. In a series of 191 patients, tumour deposits could be identified by the gamma probe in 141 (73%) patients [27]; 27 patients had occult lymph node metastases, and in 60 patients, surgical resection margins could be defined more accurately. The authors stated that in approximately 25% of cases, surgical procedures were modified on the bases of probe findings. With CC-49 (^{125}I-labelled), a second generation B.72.3 MAb, results were even better: the probe localised primary tumour in 83% and recurrent tumour in 97% of the patients. Based on probe findings, the operation plan was altered in 50% of primary and 47% of the recurrent patients [28]. However, from their data, it is not clear whether this more or less extensive surgery resulted in better patient outcome. Moreover, the results of this rather complicated technique have not yet been confirmed by other groups.

Table 2. RIT in primary or recurrent operable colorectal cancer

Author and Ref.	MAb/Isotope	Number of patients	TP[x]	FN	TN	FP	CIM[xx]
Lind [7]	Anti-CEA ^{99m}Tc	12	10 pts	–	–	2	0
Neal [15]	B 72.3 ^{111}In	12	9 pts	2 pts	–	3	?
Maguire [10]	B 72.3 ^{111}In	78	74%	?	?	8%	26%
Doerr [11]	B 72.3 ^{111}In	116	70%	?	90%	5%	25
Winzelberg [16]	B 72.3 ^{111}In	23	16 pts	1	–	4 pts	?
Kroiss [12]	Anti-CEA ^{99m}Tc	14	14 pts	–	–	–	none
Bares [13]	Anti-CEA ^{111}In	11	7 pts	4	–	2	none

TP[x], true positive; FN, false negative; TN, true negative; FP, false positive; CIM[xx], change in management of the patient.

Table 3. RIT in recurrent colorectal carcinoma, including patients with CEA rise in follow-up

Author and Ref.	MAb/Isotope	Number of patients	TP	FN	TN	FP	CIM
Hertel [8]	Anti CEA ^{99m}Tc	72	69 pts	6 sites	?	1 pt	?
Hölting [24]	Anti CEA F(ab)2 ^{131}I	42	57%	41%	28%	?	
Kroiss [12]	Anti CEA ^{99m}Tc	24	17 pts	1	12 sites	1 pt	?
Bares [13]	Anti CEA ^{111}In	16	12 pts	9 sites	?	?	?

Abbreviations as in Table 2.

Table 4. RIT in patients with CEA rise without clinical evidence of recurrence

Author and Ref.	MAb/Isotope	Number of patients	TP	FN	TN	CIM
Doerr [6]	Anti CEA ^{111}In	13	11	1	1	?
Hertel [8]	Anti CEA ^{99m}Tc	6	6	–	–	?
Doerr [11]	Anti CEA ^{111}In	10	4	3	3	?

For abbreviations see Table 2.

Our experience with RIT in colorectal carcinoma is rather disappointing. We used ^{131}I-anti-CEA antibody in 6 patients who were all false negative. The whole MAb, F(ab)2 and Fab fragments of a 17-1A MAb labelled with ^{99m}Tc, ^{131}I or ^{123}I in 10 patients revealed only two positive images. We performed RIGS in 6 patients with colorectal cancer. 3 patients received ^{99m}Tc F(ab)2, anti 17-1A MAb in whom no tumour localisation was seen. The remaining 3 had ^{125}I whole antibody: in two patients with liver metastases, tumour could not be discerned, and in the third patient, primary tumour localised well. Our limited probe findings had no influence on patient management.

CONCLUSION

Unfortunately, despite the vast amount of scientific work performed on the concept of tumour targeting with antibodies, radio-immunoscintigraphy in colorectal cancer still has to be considered as experimental. From clinical studies, it is clear that labelled monoclonal antibodies are able to visualise colorectal carcinoma deposits in approximately 70% of patients and even are able to detect previously unknown tumour localisations in approximately 10% of patients, but false negative as well as false positive results are frequently seen. Its clinical value seems limited, particularly considering the relative high costs, the labourious technique and difficulties in interpretation of the scans.

Radio-immunoguided surgery enables the detection of otherwise occult disease in a substantial number of patients with primary (10–20%) or recurrent (20–40%) operable colorectal cancer. Whether this upstaging and eventually adjusted surgery is of benefit for the individual patient has to be proven in randomised trials. Currently, the routine use of RIT for the diagnosis of patients with primary or suspected recurrent colorectal carcinoma is not warranted.

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