Radioimmunotherapy of Small Volume Disease of Colorectal Cancer Metastatic to the Liver: Preclinical Evaluation in Comparison to Standard Chemotherapy and Initial Results of a Phase I Clinical Study

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Abstract

At the time of surgery, occult metastases (micrometastases) are present in more than 50% of colorectal cancer patients, and the liver is the most frequent site of apparent metastatic disease. Frequently, adjuvant chemotherapy is unable to prevent tumor recurrence. Thus, novel therapeutic strategies are warranted. The aim of this study was to establish a model of human colon cancer metastatic to the liver of nude mice, to assess, in this setting, the therapeutic efficacies of radioimmunotherapy (RAIT) compared to standard chemotherapy and to evaluate, in a Phase I/II trial, the toxicity and therapeutic efficacy of RAIT in colorectal cancer patients with small volume disease metastatic to the liver.

Multiple liver metastases of the human colon cancer cell line GW-39 were induced by intrasplenic injection of a 10% tumor cell suspension. Whereas controls were left untreated, therapy was initiated on day 10 or 20 after tumor inoculation. In the 20-day-old tumor stage, although it prolonged life, 131I-F023C5 was unable to achieve cures, whereas 131I-MN-14 was still successful in 20%. Histologically, no remaining viable tumor cells could be demonstrated in these animals surviving > 6 months.

In the mice, untreated controls died from rapidly progressing hepatic metastases at 6–8 weeks after tumor inoculation. The life span of mice treated with 5-fluorouracil/leucovorin was prolonged for only 1–3 weeks, whereas irinotecan led to a 5–8-week prolongation. In contrast, at their respective MTDs, the 131I-labeled low-affinity anti-CEA MAb, F023C5, led to a 20% permanent cure rate, and the high affinity MAb, MN-14, led to an 80% permanent cure rate, when therapy was initiated at 10 days after tumor inoculation. In the 20-day-old tumor stage, although it prolonged life, 131I-F023C5 was unable to achieve cures, whereas 131I-MN-14 was still successful in 20%. Histologically, no remaining viable tumor cells could be demonstrated in these animals surviving > 6 months.

In patients, the MTD was reached at 60 mCi/m² of hMN-14 (at 70 mCi/m², two of three grade 4 myelotoxicities). Of 11 assessable patients, 2 had partial remissions (corresponding to an objective response rate of 18%), and 5 (45%) had minor/mixed responses or experienced stabilization of previously rapidly progressing disease.

These data suggest that in small volume disease, RAIT may be superior to conventional chemotherapy. Antibodies of higher affinity seem to be clearly superior. The clinical response rates in patients with small volume disease are encouraging, being comparable to the response rates of conventional chemotherapeutic regimens but with fewer side effects. Ongoing studies will show whether treatment at the MTD will further improve therapeutic results.

Introduction

Colorectal cancer, making up 15% of all malignancies, is one of the most frequent cancer types in both sexes (1). To date, surgery is the only potentially curative therapeutic modality (1). However, despite the introduction of adjuvant chemotherapeutic regimens, which have been shown to reduce the relapse rate by approximately 30% (1, 2), the disease will still recur in approximately one-half of the patients. In unresectable cases, the 5-year survival is close to zero (3, 4), despite several promising...
new chemotherapeutic developments, such as the introduction of the semisynthetic camptothecin derivative irinotecan as a topoisomerase I inhibitor (1, 5, 6).

Immunotherapy with the murine MAb3/CO17-1A, which is directed against a 41-kDa cell surface glycoprotein of many epithelial cells, including colorectal malignancies, has shown, in an adjuvant setting, results comparable to those obtained with adjuvant chemotherapy (7, 8). This is in contrast to its lack of significant antitumor effects in established metastatic disease (9, 10). In this context, RAIT appears as an attractive therapeutic concept, aiming to deliver tumoricidal radiation doses to tumors that may be too large for being susceptible to a purely immunological approach (11). Indeed, in radiosensitive tumors, such as non-Hodgkin’s lymphoma, RAIT has led to long-term remissions or even cures in a high percentage of treated patients (12, 13). In solid tumors, however, success is still limited, probably due to the low specific accretion of the radiolabeled antibody in the tumor target as compared to the normal tissues (11). However, as we have shown earlier, the tumor uptake, and thus the radiation dose to the tumor, increases exponentially with decreasing tumor size (11, 14, 15). Therefore, RAIT may be a viable option, especially in small volume and minimal residual disease (11, 14, 15).

In colorectal cancer, the liver is the most frequent site of apparent metastatic disease (1). The aim of the present study was, therefore, to establish a model of human colon cancer metastatic to the liver of nude mice, to compare the therapeutic efficacy of radiolabeled MAbs versus equitoxic “standard” chemotherapy with 5-FU/folinic acid (leucovorin), or irinotecan, in this xenograft model, and to evaluate, in a pilot Phase I clinical trial in colorectal cancer patients, the toxicity and efficacy of RAIT in small volume disease metastatic to the liver.

Patients and Methods

**Antibodies and Radiolabeling.** The murine MAb anti-CEA, clone F023C5, was obtained from Sorin Biomedica (Saluggia, Italy). It belongs to the IgG1 isotype and has an affinity constant of approximately 0.5 × 10⁷ liters/mol (16), whereas MN-14 is a high affinity MN-14 (Kₐ = 10⁹ liters/mol) IgG1 subtype murine anti-CEA MAb (obtained from Immunomedics, Inc., Morris Plains, NJ; Ref. 17). Preclinical and clinical experiences with these antibodies have been described previously (16–18). Both are directed against a similar class III epitope of the CEA molecule, according to the classification of Primus et al. (19). Recently, a humanized, CDR-grafted, form of MN-14, called hMN-14, has been developed and introduced in clinical trials (20). The anti-CD3 antibody, OKT3 (CILAG, Sulzbach-Taunus, Germany), was used as a nonspecific, antibody-isotype (IgG₂a)-matched control antibody (21).

Iodine-131 was purchased as sodium iodide in 0.1 M NaOH from NEN Du Pont (Bad Homburg, Germany). Radiodination was performed using the iodogen method, as described previously (21). Briefly, the antibody in PBS buffer was transferred into an iodogen-coated glass vial (500 μg of iodogen coating the inner surface of a 10-ml vial) with a magnetic stirbar placed inside. Sodium phosphate buffer, 0.5 M, pH 7.4, was added in a volume that was twice as much as the volume of the radioiodine to be used. The specific activity used was 15–20 mCi/mg. The vial was placed on a magnetic stirrer, and the activity was added in 2.5 ml of 0.4 M sodium phosphate, pH 7.4. After a stirring time of 10–15 min, Dowex 1 × 8–100 anion exchange resin (Cl⁻ form, Sigma, Deisenhofen, Germany) was added, and the incubation time was prolonged for another 5 min. Subsequently, the radiiodinated antibody was filtered through a sterile Millex-GV filter (pore size, 0.22 μm; Millipore, Molsheim, France). The quality of each preparation was tested by instant TLC and size-exclusion HPLC. The amount of unbound radioiodine was less than 2% in each preparation.

**Animal Models.** Female nude mice, 19–23 g and 4–5 weeks old, were purchased from Charles River (Sulzfeld, Germany). The human colon carcinoma cell line GW-39 was serially propagated as described in detail earlier (21, 22). Briefly, tumors were minced through a 40-mesh screen and rinsing with sterile HBSS (ICN Biomedicals, Eschwege, Germany) to yield a 20% cell suspension. A 200-μl dose of this suspension was injected s.c.

For the liver metastasis model, mice were anesthetized by i.p. injection of a mixture of 0.35 mg of 5,6-dihydro-2-(2,6-xylidino)-1H-1,3-thiazine hydrochloride (Rompun®, Bayer, Leverkusen, Germany) and 1.5 mg of ketamin hydrochloride (Ketanest®, Parke-Davis, Berlin, Germany). A small left subcostal incision was made (cf. Fig. 1), and the spleen was exposed and isolated between strips of sterile gauze soaked with alcohol. A 10% GW-39 cell suspension in HBSS was slowly injected into the spleen. Two min later, the splenic vessels were ligated, the spleen was removed, and the peritoneal cavity and abdomen were closed with staples. Multiple (as many as over 250) microscopic tumor colonies develop in the livers of such animals, reaching a size of approximately 250–500 μm at 10 days and a size of 1–2.5 mm at 20 days after tumor cell inoculation. With high reproducibility, the animals begin to lose weight by 4–6 weeks, and they eventually die at 6–9 weeks after tumor inoculation.

**Experimental RAIT and Chemotherapy.** Animals were either left untreated (controls) or injected with a single dose of naked (200 μg) or radiolabeled antibody, at their respective MTDs of radioactivity (260 μCi of 131I-MN-14 IgG or 600 μCi of 131I-F023C5 IgG). Eight to 20 (in most cases, 10) mice were studied in each treatment group. For chemotherapy, the mice received an i.v. injection of 1.8 mg of leucovorin, followed by 0.6 mg of 5-FU 1 h later (both...
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Fig. 1 Surgical procedure of the induction of liver metastases of the human colonic cancer cell line, GW-39, in anesthetized nude mice. 
(a) subcostal incision (top panel), exposure of the spleen on an alcohol gauze (middle panel), and intrasplenic injection of 100 μl of a 10% GW-39 tumor cell suspension (bottom panel). (b) ligation of the splenic vessels (top panel), splenectomy (middle panel), and stapling of the wound (bottom panel).

were obtained from Sigma), for five consecutive days each in 200 μl of saline. This is the MTD in mice determined by Blumenthal et al. (23) and confirmed in our experience as well. For irinotecan (CPT-11) chemotherapy, the mice were given a single i.v. injection of 2 mg of irinotecan hydrochloride in 100 μl of saline (Camptosar™, Pharmacia & Upjohn, Kalamazoo, MI), which has been shown to represent the single administration MTD.

Body weight was recorded weekly, and survival was monitored. The MTD was defined as the highest possible activity under the respective conditions that did not result in any animal deaths, with the next higher dose level resulting in at least 10% of the animals dying (24, 25). Total and differential leukocyte and thrombocyte counts, blood urea nitrogen, as well as glutamate oxaloacetate transaminase and alkaline phosphatase were determined on the day of therapy and at weekly intervals thereafter, as described previously (24, 25).

Initial Clinical Phase I/II RAIT in Patients with Small Volume Disease. Twelve colorectal cancer patients with small volume metastatic disease (all lesions ≤2.5 cm) were entered in a mCi/m²-based dose escalation study with the 131I-labeled humanized anti-CEA MAb, hMN-14 (human IgG1 subtype; Ref. 20). All had histologically proven, CEA-expressing colorectal cancer. None of the patients had major surgery or external beam radiation within the last 4 weeks before the study, and they had a performance status of 60 or greater on the Karnofsky scale.

After informed consent had been obtained, all patients were premedicated with 200 mg of potassium iodide daily, initiated 24 h before the antibody administration to decrease thyroid and gastric uptake. This medication was continued until the patients were removed from radiation restrictions. The radiolabeled antibody was infused during a 10–30-min period in a volume between 10 and 30 ml of sterile 0.9% NaCl containing 1.0–2.5% human serum albumin. The patients were given single injections, starting at 50 mCi/m² and escalating in 10 mCi/m² increments. Routine blood chemistry parameters, blood cell counts, and differential blood counts were obtained weekly until 8 weeks posttherapy and then monthly thereafter. Red marrow and organ toxicity was graded according to standard toxicity criteria (Common Toxicity Criteria of the National Cancer Institute; Ref. 26). Three patients were studied on each dose level, six if one or more developed a toxicity higher than grade 3. The MTD was defined in this trial as the very dose level at which ≤1 of 6 patients develop a myelotoxicity higher than grade 3.

Scanning was performed with a Picker Prism 2000™ double-headed gamma camera equipped with high-energy colima-
tors (Picker, Cleveland, OH). Anterior and posterior whole-body scans were obtained for \(^{131}I\) daily from 4 h to 240 h postinjection. MAb blood clearance rates were determined by counting samples at various times after the end of the infusion. Total-body clearance rates were determined from whole-body scans and hand-held rate meter measurements.

For organ and tumor dosimetry, regions of interest of the whole-body, organs, and visible tumors were generated from the anterior and posterior planar views. All calculations were performed using personal computer software developed for this purpose (27). The blood time-activity concentration data were fit by an exponential function to obtain the cumulated activity in the blood. The red marrow cumulated activity was calculated from the blood data by multiplying this concentration by 1500, as the assumed weight in grams of the marrow in an average adult. Time-activity curves were generated and integrated, and cumulated activities, as well as residence times, were derived (27). These data were entered into the MIRDose3 program (28), which yields the organ, red marrow, tumor, and whole-body dosimetry according to the MIRD scheme, based on derived residence times.

All patients underwent computed tomography of the chest, abdomen, and pelvis on the day before therapy, as well as 4 and 12 weeks later. Afterward, patients were evaluated at 3-month intervals, including clinical follow-up, sonography of the abdomen, whole-body computed tomography, routine blood chemistry, and tumor marker evaluations.

Therapeutic responses were graded according to oncological standard criteria (29), as follows. (a) Complete remission: stabilization of serum tumor marker (CEA) levels for at least 1 month. (b) Partial remission: at least 50% reduction in the sum of the diameters of measurable disease without appearance of new lesions and/or any new metastasis on treatment. (c) Minor/mixed response: less than 50% reduction in size of any lesion. (d) Stabilization of disease: no increase in the size of any lesion. (e) Progression: greater than 25% increase in measurable disease and/or any new metastasis on treatment.

Results

Animal Model of Human Colon Cancer Metastatic to the Liver of Nude Mice. Fig. 1 shows the most important steps in the surgical procedure for liver metastasis induction with the GW-39 cell line. After anesthesia, a 5-7-mm left subcostal incision allows for an easy approach to the spleen, which is exposed and isolated between strips of sterile gauze soaked with alcohol to prevent tumor cells from leaking into the abdominal cavity, which would result in disseminated peritoneal carcinomatosis (4). One hundred µl of a 10% GW-39 cell suspension in HBSS were slowly injected into the spleen, with subsequent ligation of the splenic vessels as early as 2 min later. After removal of the spleen, the peritoneal cavity and abdomen were closed with staples (Fig. 1).

Multiple (as many as over 250) microscopic tumor colonies develop in the livers of such animals, reaching a size of approximately 250–500 µm at 10 days and a size of 1-2.5 mm at 20 days after tumor cell inoculation (Fig. 2). In contrast to earlier liver metastases models (30–36), no immunosuppressive pretreatment was necessary to reach a virtually 100% tumor take rate. The perioperative mortality rate was below 10% in all cases. With high reproducibility, the animals lost weight by 4–6 weeks and eventually died at 6–9 weeks after tumor inoculation (cf. Fig. 4). At this time, the liver parenchyma was almost completely replaced by tumor in these animals (Fig. 2a, right panel).

Therapeutic Efficacy of RAIT versus 5-FU/Leucovorin or Irinotecan Chemotherapy in the Liver Metastasis Model. Whereas control mice were left untreated, therapy was initiated on day 10 or 20 after tumor cell inoculation. Animals either received chemotherapy with 5-FU/folinic acid or irinotecan or were given equitoxic radioimmunotherapy, each at its respective MTD. Other groups were given unlabeled anti-CEA antibodies (F023C5 or MN-14) or radiolabeled irrelevant (anti-CD3) antibody. Fig. 3 shows gamma camera images of two animals at 3 weeks after liver metastasis induction, injected either with the \(^{131}I\)-labeled low-affinity antibody, clone F023C5 (left panel) or with the \(^{131}I\)-labeled high-affinity antibody, clone MN-14 (right panel). The images clearly show much stronger uptake of the high affinity MAb, \(^{131}I\)-MN-14, as compared to the low-affinity MAb, \(^{131}I\)-F023C5.

Unresected animals died from rapidly progressing hepatic metastases within 6–9 weeks after tumor inoculation (Fig. 4). Histologically, the liver parenchyma was almost completely replaced by tumor in these animals (cf. Fig. 2). Whereas unlabeled antibody was completely ineffective and irrelevant radio-labeled IgG (\(^{125}I\)-OKT3) prolonged life for only 2–4 weeks, 5-FU/leucovorin chemotherapy led to a mean prolongation of survival of 1–3 weeks (significant at \(P < 0.05\) as compared to untreated controls, using the log rank test). In contrast, life prolongation induced by irinotecan was significantly (\(P < 0.02\)) longer (5–8 weeks, depending upon the tumor stage; Fig. 4), but irinotecan was unable to achieve permanent cures. Both radio-labeled tumor-specific radiolabeled antibodies performed significantly (\(P < 0.001\)) better, with 20–80% long-term survival (Fig. 4), again dependent upon the tumor stage. The \(^{131}I\)-labeled low-affinity anti-CEA MAb, F023C5, led to a 20% permanent cure rate, and the high affinity MAb, MN-14, led to an 80% permanent cure rate, when therapy at the respective MTDs (600 µCi of \(^{131}I\)-F023C5 versus 260 µCi of \(^{131}I\)-MN-14; Refs. 37, 38) was initiated at 10 days after tumor inoculation. In the 20-day-old tumor stage, although it prolonged life, \(^{131}I\)-F023C5 was unable to achieve cures, whereas \(^{131}I\)-MN-14 was still successful in 20%. Animals surviving 30 weeks were sacrificed, and their livers were examined histologically; no remaining viable tumor cells could be demonstrated in these animals surviving >6 months.

Initial Clinical Phase I Radioimmunotherapy in Patients with Small Volume Disease. Twelve patients with small volume disease of metastatic colorectal cancer were enrolled in a Phase I dose escalation study with the \(^{131}I\)-labeled...
Fig. 2 Development of hepatic metastases of the human colonic cancer cell line, GW-39, in nude mice. a, at 1 week post-tumor cell inoculation, the liver was macroscopically still normal (left panel); at 2 weeks, multiple metastases became apparent (middle panel), and untreated animals died at 5–6 weeks after tumor cell inoculation with a grossly enlarged liver, almost completely replaced by tumor (right panel). b, histologically, multiple (as many as over 250) microscopic tumor colonies develop in the livers of such animals, reaching a size of approximately 250–500 μm at 10 days after tumor cell inoculation (top panel) and a size of 1–2.5 mm at 20 days (bottom panel). Bar, 100 μm.

high-affinity humanized anti-CEA MAAb, MN-14. The patients’ characteristics are summarized in Table 1. Five women and seven men presented with small volume metastatic disease (defined as all lesions having less than 2.5 cm in maximum diameter). Most of them were pretreated with chemotherapy (5-FU alone or in combination with leucovorin; cf. Table 1) or external beam radiotherapy. These conventional treatment regimens either had failed or were abandoned because of severe side effects, such as mucositis and diarrhea. All but one patient had liver metastases, two had additional lung lesions, and two
Fig. 3  Scintigraphic comparison of two mice at 3 weeks after liver metastases induction injected either with 100 μCi of the 131I-labeled low-affinity antibody, clone F023C5 (left panel), or given 100 μCi of the 131I-labeled high-affinity antibody, clone MN-14 (right panel; Picker Prism 2000 gamma camera equipped with high-energy parallel hole collimators; 100 kilocounts each).

suffered from a local recurrence. Serum CEA levels were mildly to moderately elevated (range, 4.8–29 ng/ml; cf. Table 1).

The therapy infusion was tolerated well by all patients. The only acute side effect observed was an occasional mild nausea, occurring in approximately one-half of the patients, most likely caused by the stomach-irritating effects of the concomitant cold iodine blocking medication. As expected, the red marrow was the dose-limiting organ. Typically, WBC and platelet counts began to drop, platelets usually preceding leukocytes, 2–3 weeks after RAIT, reaching their nadir 4–7 weeks after the RAIT injection. The time to recovery was typically 9–11 weeks post-RAIT. At the 50 mCi/m² dose level, one patient experienced grade 1 and two experienced grade 2 leukopenia and/or thrombocytopenia. At 60 mCi/m², one patient had grade 2 myelosuppression, four had grade 3, and one had grade 4 (cf. Table 1), whereas at 70 mCi/m², two of three patients developed grade 4 toxicity. Thus, according to our previous definition, 60 mCi/m² of 131I-hMN-14 is the MTD in this patient population. No other, nonhematological or long-term normal-organ toxicities were observed within a 1-year follow-up period.

Whereas most lesions larger than 2 cm were visualized in the posttherapy gamma camera scans, smaller lesions escaped detection (Fig. 5a). Nevertheless, therapeutic results were independent of whether the lesions were visualized or not. Overall, of 11 assessable patients, 2 experienced a partial remission (corresponding to an objective response rate of 18%; 1 of the patients was still in remission after 12 months; Fig. 5), and 5 patients (45%) experienced minor/mixed responses or stabilization of their previously rapidly progressing disease, lasting from 3 up to 12+ months. An at least transient 50% drop of serum tumor marker levels (CEA, CA19–9) was observed in 9 of the 11 assessable patients. Finally, four patients progressed despite therapy. Interestingly, given the comparably low number of patients, no clear correlation between radionuclide dose levels and therapeutic response was observed.

Table 2 shows the overall whole-body and normal organ dosimetry of 131I-hMN14 IgG in these 12 patients. Mean whole-body doses were approximately 1 cGy/mCi, and mean red marrow doses were close to 3 cGy/mCi. The radiation dose estimates for the kidneys, at 3.6 ± 1.0 cGy/mCi, may be slightly overestimating the actual kidney doses, because in most in-
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Fig. 4 Survival of mice bearing GW-39 liver metastases that were left untreated (-----), were given chemotherapy with 5-FU/leucovorin (----) or irinotecan (-----), or were treated with radioimmunotherapy with 131I-labeled low-affinity (F023C5; ---) or high-affinity (MN-14; --) anti-CEA antibodies or 131I-labeled irrelevant IgG (-----) at a tumor stage of 10 (top panel) or 20 (bottom panel) days.

Discussion

Although radioimmunotherapy is an attractive concept for a more target-oriented systemic cancer therapy than is usually achieved with other forms of systemic therapies (11), its major drawback in solid tumors is the problem of achieving sufficiently high tumor uptake, and thus sufficiently high radiation doses (11). Frequently, myelotoxicity becomes dose limiting before therapeutically effective tumor doses are reached (11, 29). We and others have shown earlier that tumor uptake and radiation doses to the tumor are inversely correlated to the tumor size (11, 14, 15). This led to the hypothesis that radioimmunotherapy may be a viable therapeutic option in both small volume metastatic disease and in an adjuvant setting, although it may not be a very effective treatment modality in “bulky” disease at nonmyeloablative doses.

As compared to some earlier models of human colorectal cancer metastatic to the liver of nude mice, the GW-39 model, as presented in this communication, offers some clear advantages. One of the first liver metastases models described by Sharkey et al. (39) relied on a direct inoculation of tumor cells into the liver of unconditioned hamsters. Although 97% of the animals developed tumors at the site of injection, the tumors did not spread throughout the liver. Therefore, this model does not represent the typical metastatic process in the human situation, where mostly micro- or macroscopic tumor cells and colonies are found ubiquitously distributed over both liver lobes. Although intrasplenic models, as used in this communication, better represent the clinical setting, they often require immunosuppressive pretreatment, such as whole-body irradiation or steroid or cyclosporin A medication, to achieve sufficiently high tumor take rates (30, 31). On the other hand, such an immunosuppressive pretreatment not only is time-consuming but potentially causes higher chemo-or radiosensitivity of these animals, so that higher treatment-related toxicity may occur at lower dose levels. In contrast, the intrasplenic GW-39 model yields reliable tumor take and animal death rates, allowing for a better judgement of the therapeutic efficacy of various treatment regimens.

Our preclinical data suggest that radioimmunotherapy may be therapeutically superior to both standard 5-FU/leucovorin, the more “novel” irinotecan chemotherapy, or “cold” (i.e., unlabeled, “naked”) immunotherapeutic approaches. Similar data on the comparison of radioimmunotherapy and 5-FU chemotherapy have been reported earlier by Blumenthal and colleagues (23, 40, 41) in several s.c. human colon cancer models in nude mice. Although irinotecan was significantly more effective than 5-FU/leucovorin, it was unable to achieve cures, which is in accordance with the clinical situation (1, 3, 4). Interestingly, although most earlier studies failed to show a significant difference in uptake values or radiation doses between low- and high-affinity MAbs (reviewed in Refs. 11 and 14), our preclinical data clearly demonstrate the therapeutic superiority of high-affinity MAbs. Unfortunately, real quantitative uptake determinations are difficult in micrometastatic settings (40, 41), so at this point, we do not have an estimate of the actual radiation doses to the intrahepatic tumor colonies with both the low- and high-affinity MAbs.

In accordance with these preclinical data, toxicity in the pilot clinical radioimmunotherapy studies was restricted to a
transient myelosuppression. The lack of other organ toxicities is in agreement with other low-dose RAIT studies (see, e.g., Ref. 29). Encouraging is the fact that an almost 20% objective response rate was observed in these patients, despite the fact that most of them had failed prior chemotherapy. In an additional 45%, previously rapidly progressing disease was stabilized for up to more than 1 year after radioimmunotherapy. These results compare very favorably to the those of the most successful chemotherapeutic regimens in colorectal cancer but cause less toxicity (1, 4–6). The fact that several of these lesions could not be visualized by posttherapeutic gamma camera imaging yet responded to the treatment is not surprising, considering the study of Dunn et al. (42), who showed that, due to the suboptimal physical properties of $^{131}$I for imaging and due to the limited resolution of conventional gamma cameras, lesions may escape the scintigraphic detection, and yet they may receive therapeutically effective doses of as high as several thousand cGy (42). The fact that several of these lesions could not be visualized is the very reason why we did not attempt tumor dosimetry in the present Phase I study. The normal organ dosimetry, as reported in this communication, corresponds well to the $^{131}$I-hMN-14 dosimetry reported earlier (20). Interestingly, blood doses correlated fairly well to the resulting myelotoxicities, better than in many previous radioimmunotherapy studies (29), which may be at least partially due to a fairly homogeneous patient population with respect to chemo- and radiotherapeutic pretreatments.

In summary, our data suggest that nonmyeloablative radioimmunotherapy may be a viable therapeutic option in colorectal cancer patients with limited disease. Myelotoxicity is the only dose-limiting toxicity. Additional studies are ongoing to show whether combination approaches of radioimmunotherapy with
Fig. 5 Clinical targeting and therapeutic response in patient 4 (cf. Table 1), a 59-year-old man with liver metastases of rectal cancer who had failed 5-FU chemotherapy. a. The scan 72 h after the administration of 106 mCi (60 mCi/m²) of 131I-labeled hMN-14 (i.e., treated at the MTD) shows uptake in a 2-cm lesion in the dome of the liver. b. Therapeutic response in the same patient: the 2-cm liver metastasis (left column, before therapy) shows a good partial remission at 3 months after radioimmunotherapy (right column).
animal care. We also thank Prof. Dr. E. Grabbe, Prof. Dr. J. W. Oestmann, and Dr. D. Müller for the radiological evaluation of our patients.

Table 2 Normal organ dosimetry of $^{131}$I-hMN-14 in the patients of this Phase I dose escalation study

<table>
<thead>
<tr>
<th>Organ</th>
<th>Radiation absorbed dose (cGy/mCi) (mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td>Whole-body</td>
<td>0.98 ± 0.47</td>
</tr>
<tr>
<td>Red marrow (blood)</td>
<td>2.97 ± 1.53</td>
</tr>
<tr>
<td>Liver</td>
<td>2.35 ± 1.44</td>
</tr>
<tr>
<td>Spleen</td>
<td>3.68 ± 2.02</td>
</tr>
<tr>
<td>Lung</td>
<td>2.49 ± 1.65</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.62 ± 1.04</td>
</tr>
<tr>
<td>Thyroid</td>
<td>34.2 ± 18.5</td>
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*Red marrow dosimetry is based on blood data, assuming equal activity concentrations in red marrow and blood (29).*

References

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Clin Cancer Res 1999;5:3232s-3242s.