Treatment of Metastatic Prostate Carcinoma with Radiolabeled Antibody CC49


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A Phase II trial of 75 mCi/m² T311-anti-TAG-72 high-affinity antibody CC49 was studied in 15 patients with hormone-resistant metastatic prostate cancer. Methods: Patients had adequate renal, liver and hematopoietic function. No previous cytotoxic chemotherapy was allowed and previous radiation was limited to 20% of the active bone marrow. Results: No acute adverse reactions occurred, but all patients had evidence of an immune response to CC49 by 4 wk. Six of 10 symptomatic patients had bone pain relief, but no patients met the radiographic or PSA criteria for objective response. Positive imaging of bone and/or soft-tissue lesions was noted for 13 of the 15 patients. Conclusions: CC49 had a high frequency of tumor localization with evidence of anti-tumor effects (pain relief).

Key Words: prostate carcinoma; radiolabeled antibody


Diffuse metastatic bone lesions from prostate cancer unresponsive to hormone manipulation have been treated with systemic radionuclide therapy for more than a decade. Bone-seeking agents such as 32P, 89Sr and 153Sm have been useful for palliation of pain in patients with widespread bony metastases where conventional external beam radiation was not feasible (1–3).

A potential alternative to systemic therapy with bone-seeking radionuclides is the conjugation of radionuclides to antibodies reactive with prostate cancer-associated antigens. TAG-72 is a tumor-associated mucin of high molecular weight present in a variety of adenocarcinomas, including colon, breast, pancreas and prostate carcinomas (4). The initial anti-TAG-72 monoclonal antibody (B72.3) has been studied in its original murine form (5–11) and as a genetically engineered chimeric mouse/human molecule in radioimaging and radioimmunotherapeutic trials (12–16). A recent study has suggested that this antibody can localize to primary metastatic sites of prostate cancer (17). Second generation anti-TAG-72 monoclonal reagents have been prepared (18), and one of these (CC49) has a higher binding affinity over B72.3 and superior localization to human cancer xenografts (19). In an animal model of radioimmunotherapy, CC49 is reported to have superior therapeutic effects than B72.3 (20). Results from a Phase I trial of 131I-CC49 in patients with metastatic colorectal cancer indicated that a dose of 75 mCi/m² was tolerated with 50% of patients having Grade III or IV marrow suppression (mainly thrombocytopenia) (21). This dose of 131I-CC49 was investigated in a Phase II trial in patients with hormonally unresponsive metastatic prostate cancer.

MATERIALS AND METHODS

Clinical Protocol

Eligible patients had histologically confirmed adenocarcinoma of the prostate and had failed standard hormonal therapy. Eligibility criteria included TAG-72 positive tumor by immunoperoxidase staining, Karnofsky performance status ≥60, adequate hematologic, renal and liver function. Patients were excluded for iodine allergy, a history of cytotoxic chemotherapy, radiation to ≥20% of the active marrow, other invasive malignancies or infection with HIV or hepatitis B. Concurrent chemotherapy, radiation, immunotherapy or new hormonal therapies were not allowed. This study was reviewed and approved by the University of Alabama at Birmingham (UAB) Institutional Review Board, and all patients gave informed consent.

The trial design was an open-label Phase II study coordinated through the National Cancer Institute. After satisfactory pretherapy evaluation, patients (15 males, ages 54–80) received 50 μg Synthroid daily and 10 drops of a saturated solution of potassium iodide (SSKI, 1 g/ml) daily, beginning 2 days prior to antibody therapy and continuing for 14 days thereafter. Patients were treated in lead-lined hospital rooms at the UAB General Clinical Research Center and were confined in isolation with radiation precautions until their exposure rate at one meter was ≤5 mRem/hr. Prior to the radiolabeled dose, patients received a test dose of unlabeled CC49 (100 μg) with vital signs monitored every 10 min times three. If no signs of allergic or other adverse reactions were observed, the radioimmunoconjugate (75 mCi/m²) was infused over 1 hr with vital signs monitored every 15 min during administration and for 1 hr postinfusion.

Subsequent to therapy, patients had serial gamma camera imaging, whole-body gamma counts and blood sampling determination of immune response to the administered antibody. Follow-up

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evaluation included history and physical exam, prostate-specific antigen (PSA), prostatic acid phosphatase, blood counts, liver, renal and thyroid function studies. A pain index was used which was comprised of a pain score and a narcotic score which was derived by conversion of analgesics to an equivalent amount of parenteral morphine (22). The pain score was calculated by multiplying the frequency and severity of pain. Tumor response was assessed 6 wk post-therapy. Toxicity grading utilized the RTOG grading system (23).

Response criteria were adapted and modified from those used in cooperative group trials (24). Response criteria were defined as follows for radiographically identified lesions:

- complete regression (CR): disappearance of all evidence of tumor;
- partial regression (PR): reduction in product of longest perpendicular diameter of indicator lesions by ≥50% without progression in any lesion or appearance of new lesions (in the case of measurable osteolytic lesions, definite evidence of recalcification agreed upon by two independent investigators constituted PR);
- stable: failure to qualify for CR, PR or progression;
- progression: an increase of ≥25% in the product of longest perpendicular diameters of indicator lesions or appearance of new lesions.

Response criteria based on PSA changes were defined as follows:

- complete response: normalization of PSA in three successive determinations;
- partial response: decline of PSA level by >80% for three consecutive determinations;
- stable: PSA change <25% in 3 mo;
- progression: if baseline PSA is greater than five times the upper limit of normal, progression is defined as three consecutive increases in PSA to >50% above baseline level. If baseline PSA is less than five times the upper limit of normal, a rise of three consecutive measurements to ≥50% above five times the upper limit of normal will be considered progression;
- relapse: PSA increase of >50% over the minimum value recorded during response as seen on three successive determinations. The duration of response was measured from the achievement of that response to the first sign of relapse.

Dosimetry and Imaging Techniques

Dosimetry data collection by gamma camera imaging and whole-body gamma counts was as previously designed (25). Whole-body scans were performed on at least 3 days after radioimmunotherapy and SPECT imaging was done for one region of interest. Scan speed for a whole-body image was usually 30 cm/min on the day the patient was discharged from the hospital. Total time for both anterior and posterior whole-body views was approximately 15 min. Static (spot) images were acquired on a 128 × 128 matrix for 400K counts using a high-energy, general-purpose collimator. SPECT images were obtained with a 64 × 64 matrix using step-and-shoot tomography. To obtain approximately 40–90K counts per step, 10–30-sec stops were required. Radiation doses to tumors and organs were estimated using the MIRD formalism with data obtained from planar scintigrams of tumor sites. Gamma camera images of localization sites were reported as positive for a score of 2–4 according to the following grading scale: 0 = within normal limits; 1 = probably negative; 2 = suspicious; 3 = positive; 4 = strongly positive.

CC49 Antibody

Monoclonal antibody CC49 is an IgG1 which was obtained by immunizing mice with purified TAG-72 (18). The antibody was produced in continuous in vitro culture and was provided by the National Cancer Institute (NSC #620537, BB IND 3006) as a sterile, nonpyrogenic aqueous solution for intravenous use. Each 1.5-mL vial contained 10.69 mg/ml CC49 in preservative-free phosphate-buffered saline. Radiolabeling was performed on the day of each administration at 10 mCi/mg antibody utilizing standard iodogen methodology as previously described (25).

PSA Assay

In order to avoid variation in processing samples at seven time points over a 6-wk interval, pretreatment and weekly serum samples were assayed in the same batch using a commercially available kit. The assay was modified by preabsorption of sera with mouse IgG-coated immunoaffinity beads if the patients’ sera contained high amounts of human anti-mouse IgG which interfered with the PSA assay (26).

Statistical Analysis

Descriptive statistics were calculated for each measurement. Correlation analysis was conducted to examine the relationships among these measurements, such as age, whole-body radiation dose, prior radiotherapy, bone marrow suppression indicators, liver function and pain symptoms. General linear models (F-test) were used to test the difference of bone marrow suppression toxicity grades among groups of patients classified by age (<65 versus ≥65) and prior radiotherapy (27).

RESULTS

Fifteen men (age 54–80) with metastatic prostate cancer were treated with 75 mCi/m² 131I-CC49. All had failed hormonal therapy, and 12 of the 15 had pain related to their disease (Table 1). None had received prior cytotoxic chemotherapy or immunotherapy. Seven patients had previous radiation to a restricted volume, which accounted for ≤20% of the active marrow. One patient’s previous radiation consisted only of a 125I seed implant. No acute reactions were observed at initial therapy. Bone marrow suppression was the only consistent toxicity with transient Grade 3–4 neutropenia occurring in 6/15 patients and Grade 3–4 thrombocytopenia occurring in 9/15 patients (Table 1). There was no correlation of severity of bone marrow suppression with age (r = −0.01, p = 0.97) or presence of prior external beam radiotherapy (F = 0.31, p = 0.58). No infections or bleeding occurred, but two patients had platelet transfusions for platelet counts <25,000/mm³ and three patients received blood transfusions for hemoglobin levels of 6.8, 9.1 and 9.7 g%. Other toxicities possibly related to 131I-CC49 therapy included a transient elevation of liver function tests in Patient 10, three days of pain exacerbation preceding pain relief in Patient 7 and thyroiditis in Patient 13 who was not compliant with the use of SSKI. Patient 5 developed a rash and fever which was thought to be a reaction to Synthroid.
His symptoms resolved with discontinuation of the medication.

Only three patients had no pain symptoms from metastatic lesions prior to treatment and these patients remained pain free with stable disease ≥6 wk. Of the remaining twelve patients, two were not evaluable for pain relief, one had no change in moderate pain symptoms, three experienced worsening of pain and increased analgesic needs, while six had pain relief or decreased use of analgesics. Two of the patients (#4 and #7) that had relief were without cancer-associated pain or need for narcotic analgesics by the end of the treatment course, two patients (#11 and #14) had short-lived amelioration of pain (<6 wk), and one patient (#13), although remaining symptomatic, decreased his narcotic dose by more than half. Thus, overall 6/10 symptomatic, evaluable patients appeared to have some degree of pain relief due to \( ^{131} \text{I-CC49} \) therapy.

Although two patients showed improvement on post-treatment bone scans, no patients achieved an objective response to therapy using radiographic or PSA criteria. Ten patients were classified as stable disease, whereas four patients had progressive disease at the 6-wk evaluation time. Stable disease did not correlate with extent of tumor TAG-72 positivity, radiimmune imaging or pain relief. Stable patients were followed 2–15 mo post-therapy. All had received alternate therapy or shown evidence of progression by 6 mo. All four patients who progressed had pretherapy acid phosphatase levels of >5 ng/ml, whereas only 1/10 patients with stable disease had values >5 ng/ml. Lactic dehydrogenase levels rose in patients with progressive disease (mean increase at 160%), whereas patients with stable disease had a mean decrease of 5%. Pretherapy PSA values ranged from 9 to 15,200 ng/ml with 6-wk values that included four patients with <25% increase; three pa-

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Prior Radiation</th>
<th>% of Tumor TAG-72 Positive</th>
<th>Known Site of Disease</th>
<th>Imaging</th>
<th>Improvement of Pain</th>
<th>Whole-Body rad. dose (cGy)</th>
<th>Nadir WBC (Grade)</th>
<th>Nadir platelets (Grade)</th>
<th>Response*</th>
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<td>No</td>
<td>5–10</td>
<td>Bone/Nodes + (Bone)</td>
<td>No</td>
<td>105</td>
<td>5.9 (0)</td>
<td>179 (0)</td>
<td>Stable</td>
<td></td>
</tr>
<tr>
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<td>62</td>
<td>No</td>
<td>10</td>
<td>Nodes</td>
<td>+</td>
<td>114</td>
<td>2.7 (2)</td>
<td>42 (3)</td>
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<td></td>
</tr>
<tr>
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<td>50</td>
<td>Bone</td>
<td>+</td>
<td>123</td>
<td>1.8 (3)</td>
<td>62 (2)</td>
<td>Progression</td>
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</tr>
<tr>
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<td>&lt;5</td>
<td>Bone</td>
<td>Yes</td>
<td>92</td>
<td>4.8 (0)</td>
<td>110 (1)</td>
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<tr>
<td>5</td>
<td>55</td>
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<td>30–40</td>
<td>Bone</td>
<td>+</td>
<td>NE</td>
<td>1.8 (3)</td>
<td>28* (3)</td>
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<td></td>
</tr>
<tr>
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<td>63</td>
<td>No</td>
<td>40</td>
<td>Bone</td>
<td>+</td>
<td>NE</td>
<td>3.7 (1)</td>
<td>59 (2)</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>Yes</td>
<td>60</td>
<td>Bone</td>
<td>+</td>
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<td>3.0 (1)</td>
<td>54 (2)</td>
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<td>5–10</td>
<td>Bone</td>
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<td>133</td>
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<td>9</td>
<td>70</td>
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<td>&gt;50</td>
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<td>+</td>
<td>99</td>
<td>1.4 (3)</td>
<td>18 (4)</td>
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<td>Bone</td>
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<td>No</td>
<td>1.6 (3)</td>
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<td>65</td>
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<td>20</td>
<td>Bone</td>
<td>+</td>
<td>Yes</td>
<td>2.0 (2)</td>
<td>25 (3)</td>
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<td>64</td>
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<td>70</td>
<td>Bone</td>
<td>+</td>
<td>145</td>
<td>2.1 (2)</td>
<td>12 (4)</td>
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<td>Bone</td>
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<td>Yes</td>
<td>0.8 (4)</td>
<td>24 (4)</td>
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<td>58</td>
<td>No</td>
<td>5</td>
<td>Bone</td>
<td>+</td>
<td>Yes</td>
<td>2.8 (2)</td>
<td>40 (3)</td>
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<td>15</td>
<td>78</td>
<td>Yes</td>
<td>10–30</td>
<td>Bone</td>
<td>+</td>
<td>119</td>
<td>2.6 (2)</td>
<td>52 (2)</td>
<td>Stable</td>
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*Patient 1 was clinically stable but did not have F/U scan. Patient 5 progressed clinically but not by >25% increase in tumor size. NE = not evaluable.

FIGURE 1. Comparison of conventional bone scan and scintigraphy after injection of \(^{131} \text{I-CC49} \) in Patient 15. There is more intense skeletal activity in the conventional bone scan (A) compared to thyroid, blood pool and rib metastasis on immunoscintigraphy (B).

Prostate Carcinoma Radioimmunotherapy • Meredith et al. 1019
pated external beam radiation or doses delivered by a single administration of $\pm 3$ mCi of $^{89}$Sr.

Table 3 provides the human antibody response to CC49. All patients had an immune response, with 14/15 having a positive response by Day 14 postinfusion and 12/15 developing large amounts of antibody binding activity (>1000 ng/ml).

**DISCUSSION**

This study represents an analysis of an anti-TAG-72 monoclonal antibody in immune localization and/or therapy of prostate cancer. Most trials with B72.3 or second generation CC49 have been carried out in gastrointestinal malignancies (5-9,21,28). The frequency of positive radioimmunological imaging with this antibody (13/15 patients or 87%) appears comparable to or better than that reported for other prostate-reactive monoclonal antibodies, including cyt-356 (29), anti-prostate-specific antigen (30) or anti-prostatic acid phosphatase (31). As seen in these previous trials, $^{131}$I-CC49 detected fewer lesions than standard $^{99m}$Tc bone scans but has the ability to detect sites of metastases outside of the skeleton. The relationship between the extent of TAG-72 expression in tumor speci-

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**TABLE 2**

Iodine-131-CC49 Dosimetry Estimates for Selected Tumor Sites

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Site</th>
<th>Tumor mass (g)</th>
<th>$T_{1/2}$ (Hr)</th>
<th>Tumor dose (cGy)</th>
<th>Dose/Activity (cGy/mCi)</th>
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<tbody>
<tr>
<td>5</td>
<td>Pelvis</td>
<td>156</td>
<td>41.7</td>
<td>208</td>
<td>1.4</td>
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<tr>
<td>7</td>
<td>Shoulder</td>
<td>82</td>
<td>66.3</td>
<td>243</td>
<td>1.6</td>
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<tr>
<td>11</td>
<td>Femur</td>
<td>69</td>
<td>36.0</td>
<td>457</td>
<td>2.6</td>
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<tr>
<td>15</td>
<td>Rib</td>
<td>73</td>
<td>39.5</td>
<td>1083</td>
<td>7.9</td>
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**TABLE 3**

Immune Response to m-CC49 in Prostate Cancer

<table>
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<tr>
<th>Patient no.</th>
<th>Pretherapy</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3/4</th>
<th>Week 5/6</th>
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<tr>
<td>1</td>
<td>26</td>
<td>103</td>
<td>590</td>
<td>1,531</td>
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<tr>
<td>2</td>
<td>16</td>
<td>18</td>
<td>19</td>
<td>164</td>
<td>109</td>
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<tr>
<td>3</td>
<td>13</td>
<td>23</td>
<td>508</td>
<td>3,064</td>
<td>23,120</td>
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<tr>
<td>4</td>
<td>18</td>
<td>179</td>
<td>1,396</td>
<td>1,421</td>
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<td>13</td>
<td>16</td>
<td>2,399</td>
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<td>17</td>
<td>11,743</td>
<td>26,299</td>
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<td>29</td>
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<td>2,657</td>
<td>6,926</td>
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<td>11</td>
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<td>97</td>
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<td>40</td>
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<td>102</td>
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<td>9</td>
<td>9</td>
<td>11,540</td>
<td>3,276</td>
<td>8,080</td>
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<tr>
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<td>171</td>
<td>424</td>
<td>1,060</td>
<td>1,220</td>
<td>1,200</td>
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<td>5</td>
<td>3,674</td>
<td>7,179</td>
<td>14,360</td>
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<td>5</td>
<td>20</td>
<td>132</td>
<td>83</td>
<td>4,640</td>
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<tr>
<td>15</td>
<td>7</td>
<td>6</td>
<td>3,299</td>
<td>1,460</td>
<td>1,221</td>
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</table>

*Results are expressed as ng of $^{125}$I-murine CC49 bound/ml sera.
mens detected by immunoperoxidase technique on formalin-fixed tissues and positive immune localization is unclear. The two patients who failed to have a positive scan had weak TAG-72 positivity (<10% of tumor), whereas three patients with similar TAG-72 expression had positive imaging studies. This may reflect heterogeneity among lesions for TAG-72 expression, which has been previously noted (12,32). Due to assumed heterogeneity and the limited size of biopsy specimens, patients were considered eligible with as little as 2% of cells showing TAG-72 reactivity.

This study utilized a dose of $^{131}$I-CC49 (75 mCi/m²) which had been established from a Phase I trial in metastatic colorectal carcinoma patients (21). There were concerns about using this dose in patients with metastatic prostate carcinoma who are generally older and have a higher frequency of bone/bone marrow metastasis than colorectal cancer patients. However, the severity and transient nature of marrow suppression in this trial was similar to that seen in the Phase I trial. In addition, Murray et al. recently reported (28) a Phase II trial of $^{131}$I-CC49 in metastatic colorectal cancer and we compared their marrow suppression scores with the prostate carcinoma patients in this report. As illustrated in Figure 2, the degree of marrow suppression was remarkably similar. Thus, the prostate cancer patient’s marrow seems to tolerate radiation via radiolabeled antibodies comparable to patients without bone metastases. It is also interesting that there was no correlation of bone marrow suppression with increasing age, prior limited radiotherapy or extent of bone metastasis demonstrated by bone scan or radiolabeled antibody localization. In fact, our two oldest patients (ages 78 and 80) both had bone metastasis and limited prior radiotherapy. They tolerated radioimmunotherapy with modest bone marrow suppression (Grade 1–2).

The lack of objective anti-tumor responses in this trial is similar to the experience of radiolabeled antibody trials in other solid tumor disease states reflecting the relative radiore sistance of these tumors and the limited doses of radiation being delivered (21,28,33,34). The estimates of radiation dose delivered in this trial are well below doses of fractionated external beam radiation expected to produce tumor control and similar to those reported in other trials in solid tumor patients (35). Despite low radiation doses, the reduction in pain symptoms may reflect modest anti-tumor effects, even for some lesions that did not localize excess levels of radiolabeled antibody. Most symptomatic lesions that targeted were palliated, although the overall palliative response rate was less than that reported with bone-seeking radionuclides such as $^{32}$P, $^{89}$Sr and $^{153}$Sm (1–3). However, these agents are unable to treat extraosseous sites of disease. Thus, continued research attempts to exploit tumor localizing radioisotope delivery systems remains a priority.

The degree of immunogenicity seen in this trial was surprising since 13–20 mg of antibody was administered. All patients developed a rapid antibody response, with 14/15 patients having circulating levels of anti-murine monoclonal antibody by Week 2 (Table 3) and 12/15 achieving very high levels of antibody activity (>1000 mg/ml). This is in striking contrast to the experience with cyt-356, where the incidence of antibody response was <10% to antibody doses of ≤0.5 mg in the majority of patients (29). The rapid antibody response to murine CC49 will interfere with attempts at administration of a second course of therapy or to dose fractionation studies (28,36,37). Genetic engineering to decrease antigenicity, as applied to other murine antibodies, may overcome this drawback of the CC49 antibody.

Thus, this Phase II trial of $^{131}$I-CC49 failed to produce objective anti-tumor responses but did produce a high frequency of $^{131}$I localization to tumor sites and several examples of symptomatic improvement in bone pain. The use of alpha interferon in conjunction with $^{131}$I-CC49 in order to increase TAG-72 expression in tumors (38) and the use of cyclosporine to allow dose fractionation (39) in patients with hormone resistant metastatic prostate cancer are currently under investigation. Other alternatives such as ad-

![Figure 2. Comparison of toxicity of prostate cancer patients receiving 75 mCi/m² $^{131}$I-CC49 (UAB) with a group of colorectal cancer patients who received the same treatment at another institution (MDA) (29). The toxicity sum is the toxicity grade for neutropenia plus the toxicity grade for thrombocytopenia for each individual patient. Each symbol represents one patient.](image-url)
juvant use of radiosensitizers or methods that would allow dose escalation may improve efficacy.

Thyroid uptake after administration of radioactive iodine conjugated agents occurs with both tracer and therapeutic doses. This is reduced but not eliminated by blocking with synthroid and SSKI. Abnormal thyroid function test values have been observed after SSKI blocking for one-third of patients. The median time was 32 mo after high-dose therapy (40). However, to date, any clinical side effects from thyroid injury have been inconsequential compared to other potential toxicities in the management of life-threatening malignancies.

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