Radioimmunotherapy of Small Cell Lung Carcinoma with the Two-Step Method Using a Bispecific Anti-Carcinoembryonic Antigen/Anti-Diethylenetriaminepentaacetic Acid (DTPA) Antibody and Iodine-131 Di-DTPA Hapten: Results of a Phase I/II Trial

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Abstract

As small cell lung carcinoma (SCLC) is frequently a widespread disease at diagnosis, highly radiosensitive and often only partially responsive to chemotherapy, radioimmunotherapy (RIT) would appear to be a promising technique for treatment. We report the preliminary results of a Phase I/II trial of RIT in SCLC using a two-step method and a myeloablative protocol with circulating stem cells transplantation. Fourteen patients with proved SCLC relapse after chemotherapy were treated with RIT. They were first injected i.v. with a bispecific (anti-carcinoembryonic antigen/anti-diethylenetriaminepentaacetic acid) monoclonal antibody (20-80 mg in 100 ml of saline solution) and then 4 days later with di-(In-diethylenetriaminepentaacetic acid)-tyrosyl-lysine hapten labeled with 1.48-6.66 GBq (40-180 mCi) of I-131 and diluted in 100 ml of saline solution. In patients receiving 150 mCi or more, circulating stem cells were harvested before treatment and reinfused 10-15 days later. Treatment response was evaluated by CT and biochemical data during the month before and 1, 3, 6, and 12 months after treatment. All patients received the scheduled dose without immediate adverse reactions to bispecific antibody or I-131 hapten. Toxicity was mainly hematological, with two cases of grade 2 leukopenia and three cases of grade 3 or 4 thrombopenia. Body scanning 8 days after injection of the radiolabeled hapten generally showed good uptake at the tumor sites. Estimated tumor dose was 2.6-32.2 cGy/mCi. Among the 12 patients evaluated to date, we have observed 9 progressions, 2 partial responses (one almost complete for 3 months), and 1 stabilization of more than 24 months. Efficiency and toxicity were dose-related. The maximal tolerable dose without hematological rescue was 150 mCi. These preliminary results are encouraging, and dose escalation is currently continuing to reach 300 mCi. RIT should prove to be an interesting therapeutic method for SCLC, although repeated injections and hematological rescue will probably be required, as well as combination with other treatment modalities.

Introduction

SCLC represents 15-20% of all bronchogenic carcinoma diagnosed in France (1) and the United States (2). Over the past 15 years, multimodality treatment, including multimagent chemotherapy, has led to an improvement in survival, but the efficacy of SCLC treatment remains limited despite high response rates to chemotherapy and radiotherapy. The use of combined chemotherapy and thoracic radiation therapy for limited SCLC enhances local control and improves survival (3); prophylactic cranial irradiation reduces the frequency of clinically significant brain metastases and should be proposed to patients achieving a complete response (4), whereas surgery may benefit a small number of patients with stage 1 tumor (5). However, 2-year survival is usually less than 25%, even in limited disease, and fewer than 10% of patients are alive and free of disease at 5 years (6-8).

RIT is an internal radiotherapy approach in which radionuclide-labeled monoclonal antibodies recognizing tumor-associated antigens are administered systemically for selective targeting of radioactivity to tumor cells. Very encouraging results have already been obtained in NHML with or without myeloablation with iodine-131-labeled anti-CD20 monoclonal antibodies (9-12).

However, some well-known limitations of RIT are mostly problematic for solid tumor. In particular, nonspecific activity in normal tissues is usually too high compared to tumor uptake, providing an inadequate tumor:nontumor ratio that limits the rate of injected activity (13, 14). The AES has been proposed to increase the tumor:nontumor ratios. AES consists in a two-step


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3 The abbreviations used are: SCLC, small cell lung carcinoma; RIT: radioimmunotherapy; AES: affinity enhancement system; Bs: bispecific; Ab, antibody; MAb, monoclonal Ab; HAMA, human antimouse antibodies; CEA, carcinoembryonic antigen; BMT, bone marrow transplantation; NHML, non-Hodgkin malignant lymphoma; DTPA, diethylenetriaminepentaacetic acid; CT, computed tomography.
method using a BsAb and a bivalent radiolabeled hapten (15, 16). Dosimetric studies in patients have confirmed the possible therapeutic benefit of this method (17).

The present Phase I/II dose escalation trial was undertaken to evaluate the feasibility and toxicity of the method. Response to treatment was evaluated as a secondary goal of the study.

Patients and Methods

Patients. Eligible patients were adults with histologically proved SCLC expressing the CEA antigen (at least 40% of tumor cells expressing CEA on a biopsy specimen), who had failed at least on one prior chemotherapy regimen and had assessable and measurable disease. Detailed patient selection criteria are indicated in Table 1.

Reagents. A Bs anti-CEA/anti-DTPA-indium Ab (BsMAB anti-CEA/anti-DTPA-In) designated F6-734 was obtained by coupling an equimolar quantity of a Fab′ fragment of anti-CEA MAb F6 (murine IgG1 K, specific for human CEA) to a Fab fragment of anti-DTPA-In MAB 734 (murine IgG1A, specific for DTPA-In complexes) previously activated by o-phenylenediamineimide.

The bivalent DTPA hapten N-α-DTPA-tyrosyl-n-ε-DTPA-lysine (di-DTPA) was obtained by reaction of DTPA dihydridine with tyrosyl-lysine diacetate (18). 131I-bivalent hapten (131I-di-DTPA-In) was provided by Cis Bio-International (Saclay, France). Before labeling, DTPA bivalent hapten was saturated with indium in an indium chloride solution because MAB 734 only recognizes the DTPA-In complex.

AES Therapeutic Protocol and Dose Escalation Protocol. The aim of this Phase I/II study was mainly to determine the maximal tolerated dose. For this purpose, dose escalation was performed, starting from 1.85 GBq (50 mCi) of 131I-di-DTPA-In and increasing by 1.85-GBq steps.

The two-step method has been described elsewhere (15). Briefly, during the first step at day 0 (D0), nonlabeled Bs anti-CEA/anti-DTPA Ab was injected at a dose of 1 mg of Ab for 4 nmol (74 MBq) of 131I-hapten in a 100 ml serum saline infusion. Four days later (day 4), the second step consisted in injecting di-DTPA-tyrosyl-lysine bivalent hapten labeled with iodine-131. The 131I-hapten was injected in serum saline through a radioprotected device (Percufix, Cis Bio-International). Infusion was performed inside a lead-protected room in which patients remained until the dose rate became less than 20 μSv at 1 m. To protect the thyroid gland from inappropriate irradiation, the patient received 30 drops of saturated solution of potassium iodine p.o. three times daily, beginning 3 days before injection of 131I-hapten and then for 14 days after therapy.

Toxicity Monitoring. Toxicity was assessed from clinical and biological data, i.e., blood cell count, liver enzyme level (aspartate aminotransferase, alanine aminotransferase, γ glutamyl transpeptidase, alkaline phosphatase, and lactate dehydrogenase), blood biochemistry (ura, creatinine, glucose, total bilirubin, total proteins, and albumin), and urine parameters (protein, WBCs, and RBCs).

Hematological Rescue. During the first course of the protocol, it appeared that hematological toxicity was problematic for injected activities above 5.55 GBq (150 mCi). Thus, the protocol was modified, with the approval of the local ethics committee, to perform autologous BMT with peripheral stem cells. Stem cells obtained by cytophresis after stimulation by granulocyte macrophage colony-stimulating factor (10 μg/kg of body weight for 5 days) were systematically harvested before RIT for doses of 150 mCi or more. RIT was then performed if more than 1.5 × 106 stem cells (CD34+)/kg were obtained; if not, the injected activity was reduced to 100 mCi. When BMT was scheduled, stem cells were reinfected as soon as blood activity became lower than 1 μCi/ml.

Treatment Effectiveness. Response to treatment was evaluated by clinical data, morphological imaging (CT, ultrasound, and sometimes magnetic resonance imaging), and biological data (CEA and neuron-specific enolase serum levels). Response categories were defined as follows. A complete response (CR) was defined as the disappearance of all clinical and radiological evidence of disease, together with negative CEA and neurone-specific enolase serum blood levels, lasting a minimum of 1 month. A partial response (PR) was defined as a decrease of 50% or more in the size of all of the measurable lesions lasting at least 1 month. A minor response (MR) was defined as a decrease of less than 50% and more than 25% in the size of all of the measurable lesions, lasting for at least 1 month. Stable disease (SD) was defined as a less than 25% decrease or a less than 25% increase in size lasting for at least 1 month. Disease progression (PD) was defined as an increase of greater than 25% of the cross-sectional area of one or more lesions or the occurrence of new lesions irrespective of response elsewhere.
Table 2 Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Disease spread</th>
<th>[ACE] ng/ml</th>
<th>[NSE] ng/ml</th>
<th>Previous treatments</th>
<th>Residual disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>M</td>
<td>65</td>
<td>D*</td>
<td>135.1</td>
<td>19.5</td>
<td>(Cisplatin-VP16) ×6</td>
<td>Right lung, mediastinal mass and lymphnodes</td>
</tr>
<tr>
<td>02</td>
<td>F</td>
<td>61</td>
<td>D</td>
<td>1.7</td>
<td>20</td>
<td>(Adria-cyclophosphamide-vincristine) ×2</td>
<td>Left lung, mediastinum, liver</td>
</tr>
<tr>
<td>03</td>
<td>M</td>
<td>46</td>
<td>D</td>
<td>1.6</td>
<td>8.5</td>
<td>(Cisplatin-VP16) ×3</td>
<td>Mediastinum, lungs, liver</td>
</tr>
<tr>
<td>04</td>
<td>M</td>
<td>59</td>
<td>D</td>
<td>4.5</td>
<td>74.7</td>
<td>(Adria-cyclophosphamide-vincristine) ×4</td>
<td>Mediastinum</td>
</tr>
<tr>
<td>05</td>
<td>F</td>
<td>67</td>
<td>D</td>
<td>4.3</td>
<td>9.6</td>
<td>(Epirubicin-Isofamide-vepeside) × 4</td>
<td>Neck lymphnodes</td>
</tr>
<tr>
<td>06</td>
<td>M</td>
<td>66</td>
<td>L</td>
<td>19.4</td>
<td>18.2</td>
<td>(Cisplatin-VP16-cyclophosphamide) × 6</td>
<td>Liver, bone metastases</td>
</tr>
<tr>
<td>07</td>
<td>M</td>
<td>56</td>
<td>L</td>
<td>0.8</td>
<td>5.8</td>
<td>(I josamide-uromitexan) × 3</td>
<td>Right lung mass</td>
</tr>
<tr>
<td>08</td>
<td>M</td>
<td>50</td>
<td>D</td>
<td>264.1</td>
<td>16.7</td>
<td>(Cisplatin-VP16) × 6</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>09</td>
<td>M</td>
<td>60</td>
<td>D</td>
<td>4.4</td>
<td>19.5</td>
<td>(Cisplatin-VP16) × 6</td>
<td>Left lung mass</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>71</td>
<td>D</td>
<td>6.4</td>
<td>12</td>
<td>(Cisplatin-VP16) × 6</td>
<td>Mediastinal lymph nodes, liver</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>63</td>
<td>L</td>
<td>1,015</td>
<td>5.3</td>
<td>(Adria-cisplatin-VP16) × 12</td>
<td>Mediastinal lymph nodes and tumor mass</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>50</td>
<td>D</td>
<td>1,280</td>
<td>137.9</td>
<td>(Farorubicin-cisplatin-VP16- cyclophosphamide) × 6</td>
<td>Mediastinum and lung tumor mass</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>64</td>
<td>L</td>
<td>3</td>
<td>28.1</td>
<td>(Adria-cyclophosphamide-VP16) × 6</td>
<td>Liver and bone metastases</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>48</td>
<td>L</td>
<td>3.5</td>
<td>7</td>
<td>(Cisplatin-VP16) × 6</td>
<td>Mediastinum and lung tumor mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Taxotere × 3</td>
<td>Neck lymph nodes</td>
</tr>
</tbody>
</table>

* D, diffuse; L, localized disease, limited to the thorax.

**Dosimetric Studies.** The radiation dose delivered to tumor sites and normal organs was estimated by daily serial whole-body scanning. Cumulative activity in whole-body, tumor, liver, and kidneys was determined by whole-body quantitative scintigraphy performed with a double-headed Sopha Medical camera (DHD Body Track) equipped with a high-energy collimator, as proposed by DeNardo et al. (19). Whole-body scintigraphic images (anterior and posterior views) were recorded 5 min after injection of 131I-labeled hapten and then at days 1, 2, 3, 4, and 7, using a 20% window set on the 131I photopeak (364 keV). The positioning of the patient was done in a reproducible manner using a system based on laser sources.

The attenuation correction factor was determined from a transmission image. A collimated linear source perpendicular to the direction of scanning movement was attached to the lower camera head. To define the geometrical parameters for recordings, acquisition was performed in the presence and then the absence of the patient on the day of nonradiolabeled F6-734 BsMAb injection.

The geometrical mean of each acquisition was calculated and multiplied by the attenuation correction factor to obtain the resulting image. During each acquisition, a known activity standard was placed on the examination table at the level of the patient's feet to determine the calibration factor for the camera (in counts per MBq in the air). The activities calculated at the different time points were transferred to a pharmacokinetic study program (Siphar, Simed) to determine the effective half-lives of 131I-labeled hapten in the regions defined and then the cumulative activity.

The doses absorbed by tumor targets and normal tissues after injection of 131I-labeled hapten were calculated according to the medical internal radiation dose scheme (20).

Dosimetry was performed on scintigraphically visualized tumors for which it was possible to define a target volume (and thus estimate the mass) from CT scan sections. Regions of interest were defined on the liver and left kidney of each patient to estimate the doses delivered to these organs.

The calculation of the bone-marrow dose was performed according to the technique of DeNardo et al. (21) by summing a "whole-body" component of the bone-marrow dose (only penetrating radiations were taken into account) and a blood component (only nonpenetrating radiations were taken into account).

**Bioethical Considerations.** All patients received detailed information and gave their signed written consent before being included. The protocol was approved by the local ethics committee, according to European regulations.

**Results**

Fourteen patients were included and completed the treatment. All patients had previously received at least one course of chemotherapy and were in relapse of the disease. Patient characteristics are shown in Table 2.
Tumor Targeting and Dosimetry. Tumor targeting was generally excellent, all tumoral sites being visualized with high contrast, even in case of very widespread disease (Fig. 1). The retention time of radioactivity in the tumor was good and, in some cases, excellent; indeed, the biological half-life of radioactivity in the tumor was between 4.5 and 22 days. Tumor:blood ratios ranged between 0.64 and 5.8, and tumor:liver ratios ranged between 0.46 and 6.6 at day 7.

Dosimetric data were available for six patients. Mean dosimetric values are indicated in Table 3. The estimated tumor dose was between 1.81 and 32.19 cGy/mCi, depending on tumor mass and tumor uptake, but also on the biological half-life of radioactivity in the tumor. The maximum dose (32.2 cGy/mCi) delivered to the tumor in terms of cGy/mCi was obtained with the first level of activity in patient 5, who received 1.55 GBq (42 mCi) of hapten, producing a calculated total tumor dose of only 13.5 Gy.

For other tissues, greater doses were given to kidneys, according to the elimination of the radiolabeled hapten, and to red bone marrow, which accounted for the toxicity.

Toxicity. Limiting toxicity was hematological (Table 4). We observed four cases of grade III or IV leukopenia and 7
cases of grade III or IV thrombopenia. Typically, thrombopenia occurred earlier and persisted longer than leukopenia. No other significant adverse events were observed.

Response to Treatment. Twelve patients were fully evaluated (for the other 2 patients, follow-up was less than 3 months). Among these 12 patients, we observed 9 progressions, 2 partial responses (1 almost complete, but unfortunately lasting only 3 months), and 1 stabilization of more than 24 months. One patient (patient 12) was enrolled on a compassionate basis and thus was not taken into account for evaluation of efficacy.

The patient who presented disease stabilization for more than 24 months (patient 3, Fig. 2) was a 46-year-old male. Pulmonary and mediastinal lesions, which were in progression before RIT, as compared to previous CT, were unchanged 1 year after RIT was performed.

In the first patient who presented a partial response (patient 7, Fig. 3), lesions had decreased by more than 60% 3 and 6 months after RIT. This effect occurred quite late, differing from effects usually obtained with conventional radiotherapy, and persisted after 17 months, at which time the patient died from heart failure without evidence of disease progression.

The patient who exhibited almost complete response for 3 months (patient 9) had residual disease consisting only in several small liver metastases (less than 1 cm in diameter). Most of these lesions had disappeared 6 weeks after RIT (Fig. 4). Unfortunately, recurrences were detected after 3 months in liver and brain.

HAMA Response. In most cases, survival was too short to allow a good evaluation of HAMA occurrence. Among five complete evaluations, one patient showed significant HAMA levels after 2 months, which persisted at 12 months.

Discussion

RIT is a new potentially useful method of treating disseminated, radiosensitive tumors for which chemotherapy, despite significant responses, cannot provide a complete cure. Impressive results have been obtained in NHMLs using anti-CD20 antibodies labeled with iodine-131 (9–11). An overall and complete response rate of respectively 79 and 50% was obtained with nonmyeloablative activities of 131I-labeled anti-CD20 Ab.

SCLC is another type of cancer for which RIT could
Table 5  Response to treatment and clinical outcome

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Injected activity, GBq (mCi)</th>
<th>Estimated tumor dose</th>
<th>Tumor response and clinical outcome</th>
<th>Survival after RIT (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>3.58 (96.8)</td>
<td>NA*</td>
<td>Progression: death</td>
<td>109</td>
</tr>
<tr>
<td>02</td>
<td>1.18 (32)</td>
<td>NA</td>
<td>Progression: death</td>
<td>63</td>
</tr>
<tr>
<td>03</td>
<td>3.64 (98.3)</td>
<td>NA</td>
<td>Stable (&gt;24 months)</td>
<td>800</td>
</tr>
<tr>
<td>04</td>
<td>1.61 (43.6)</td>
<td>80/473</td>
<td>Progression: death</td>
<td>48</td>
</tr>
<tr>
<td>05</td>
<td>1.55 (42)</td>
<td>1352</td>
<td>Progression: death</td>
<td>92</td>
</tr>
<tr>
<td>06</td>
<td>3.90 (105.5)</td>
<td>274</td>
<td>Progression: death</td>
<td>193</td>
</tr>
<tr>
<td>07</td>
<td>4.76 (128.8)</td>
<td>2286</td>
<td>Partial response: 60% decrease of tumor size (20 months)</td>
<td>583</td>
</tr>
<tr>
<td>08</td>
<td>1.86 (50.3)</td>
<td>NA</td>
<td>Progression: death</td>
<td>34</td>
</tr>
<tr>
<td>09</td>
<td>5.03 (136)</td>
<td>NA</td>
<td>D30: partial response (&gt;50%) of multiple liver metastases; occurrence of brain metastases</td>
<td>165</td>
</tr>
<tr>
<td>10</td>
<td>4.62 (125)</td>
<td>NA</td>
<td>Progression: death</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>5.91 (159.7)</td>
<td>3664</td>
<td>Rapidly growing tumor before inclusion; progression: death</td>
<td>127</td>
</tr>
<tr>
<td>12</td>
<td>2.78 (75.1)</td>
<td>NA</td>
<td>Enrolled on a compassionate basis (life expectancy &lt;9 weeks); progression: death</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>5.74 (155.2)</td>
<td>NA</td>
<td>Progression: death</td>
<td>&gt;60</td>
</tr>
<tr>
<td>14</td>
<td>6.66 (180)</td>
<td>NA</td>
<td>D30: minimal response (-20%)</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

* NA, not applicable.

Fig. 2  Patient 3. This patient experienced disease stabilization for more than 12 months. Lesions that were in progression before RIT, as compared to previous CT, were unchanged in subsequent examinations after RIT was performed. After 24 months, the clinical status of this patient was unchanged.

provide beneficial additional treatment. Despite a high response rate since the introduction of platinum and multidrug regimens, chemotherapy has led to durable complete remission in less than 20% of cases, even in localized intrathoracic forms (22).

Preliminary studies have been conducted with various antibodies, such as anti-GD2 ganglioside MAb 3F8 (23), MOC-31 (24), and anti-neural cell adhesion molecule antibodies (25, 26). However, no clinical results appear to have been reported with RIT for SCLC.

Toxicity. The AES method provided high tumor:whole-body, tumor:liver, and tumor:blood ratios, as well as a favorable tumor:red marrow ratio, whereas limiting toxicity was hematological with severe leukopenia and thrombopenia occurring when injected activity was greater than 5.55 GBq (150 mCi), which required autologous BMT. This hematological toxicity could be partially explained by bone marrow tumor involvement, which is frequent at advanced stages of the disease.

Dosimetry and Clinical Response. Three significant responses were obtained in 12 evaluable patients. The total tumor dose, which depended on injected activity as well as tumor uptake and the retention time of radiolabeled hapten, was significant, but probably not sufficient for a tumoricidal effect (the maximum calculated dose was 36 Gy).

At least three parameters may account for the dose received by the tumor, i.e., tumor uptake and the tumor:non tumor ratio, retention time of radioactivity in the tumor, and injected activity. In solid tumors (with the exception of lymphoma), RIT is generally limited by a low tumor:tissue uptake ratio, which reduces injected activity and the dose delivered to tumor to spare other tissues from excessive toxicity. Moreover, in many cases, the retention time of radiolabeled antibodies in tumor is of short duration. The AES method improves both of these limiting parameters (15). The tumor:non tumor tissue ratio is increased, mainly because nonspecific activity is reduced, which has been demonstrated with radioimmunodetection using $^{111}$In-labeled bivalent hapten for immunoscintigraphy of medullary thyroid carcinoma (27) and non-SCLC (28), and in animal studies (29). In addition, the retention time in tumor is increased, which, in

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Fig. 3  a, left, this patient (patient 7) had a left pulmonary residual tumor before RIT (arrow). Right, after RIT, a significant decrease (greater than 50%) in the tumor mass was observed, and the case was considered as a partial response. This effect occurred late, reached 60% of decrease at 6 months, and persisted after 17 months (arrow). b, control scan performed 3 days after injection of the labeled hapten, showing the good targeting of the tumoral site, providing a dose of 17.7 cGy/mCi. This patient received 129 mCi; thus, the total dose to the tumor could be estimated as 22.8 Gy.

The present study, was especially favorable in some cases, reaching 32.2 days.

In the present Phase I/II trial, treatment efficiency was not the main objective, and only three responses were obtained, probably because of the low injected activities. In terms of cGy/mCi, the maximum dose delivered to tumor was obtained with 1.55 GBq (42 mCi) of hapten, providing a total tumor dose of only 13.5 Gy, which probably accounted at least in part for the observed progression of disease in this patient. Conversely, the three significant responses we observed were all obtained for injected activities greater than 3.7 GBq (100 mCi). If only patients injected with a dose of 3.7 GBq or more are considered, the response rate was three of seven evaluable patients (42.8%).

Such results are satisfactory in a Phase I/II trial and justify the continuation of this therapeutic approach, to improve the dose delivered to tumor. If sufficient dose levels are obtained, the therapeutic benefit of internal irradiation could be extrapolated from that of external beam radiation on the thorax, which provides an increase of 5–15% in relapse-free survival in localized forms (3, 22). For this purpose, two complementary strategies may be proposed. First, injected activity could be increased. Our study shows that in cases in which circulating stem cells could be harvested (in fact, bone marrow is often impaired after chemotherapy), more than 200 mCi could be given without significant nonhematological adverse effects. Thus, dose escalation studies are continuing to reach a level of 300 mCi.
Second, injections could be repeated, as in NHML. The possibility of repeating injections depends on the absence of HAMA. However, in the present study, follow-up was too short in most cases to have a correct evaluation of the frequency of HAMA occurrence. In another study concerning medullary thyroid carcinoma, HAMA was found in 9 of 17 patients (53%). In any event, BsAb will be totally humanized in the near future, so that HAMA should no longer be a problem with repeated injections.

RIT, like internal radiotherapy in general, is more efficient when tumor targets are smaller, i.e., less than 1 cm in diameter (13). For this reason, patients enrolled in the present Phase I study, who generally had a large tumor burden after proved chemotherapy failure, did not represent the best population for the RIT success. The method would probably be more efficient if applied together with chemotherapy (either at the same time or immediately after), to eradicate microscopic or subclinical residual disease. Interestingly, the best response in our study was obtained for minimal residual lesions (liver metastases less than 1 cm in diameter). Unfortunately, the patient who had no prophylactic brain irradiation died from brain metastases that appeared 1 month after RIT.

Our study confirms the putative interest of RIT in SCLC and indicates that the AES method could contribute to better efficacy by providing lower toxicity together with high tumor uptake, thereby allowing injection of activities that produce a significant tumoricidal effect. The AES method will probably prove useful in the future in association with other modalities.

Fig. 4 Patient 9. Almost complete response for 3 months. Residual disease in this patient consisted only small liver metastases (arrows), most of which disappeared 6 weeks after RIT. Unfortunately, recurrences were detected after 3 months, in liver and brain.

References


Radioimmunotherapy of Small Cell Lung Carcinoma with the Two-Step Method Using a Bispecific Anti-Carcinoembryonic Antigen/Anti-Diethylenetriaminepentaacetic Acid (DTPA) Antibody and Iodine-131 Di-DTPA Hapten: Results of a Phase I/II Trial

Jean-Philippe Vuillez, Françoise Kraeber-Bodéré, Denis Moro, et al.


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