Up until recently, the overall median survival of patients with high-grade gliomas usually has been less than 1 year after diagnosis (1, 2). Standard treatment consists of surgical resection of the tumor followed by radiation and chemotherapy. Although such treatment has generally increased life span by several months, the tumor inevitably recurs (3, 4) and long-term survivors are extremely rare. Recently, however, Stupp et al. (5) have reported that the combination of temozolomide and radiotherapy, followed by repetitive cycles of temozolomide alone, significantly prolonged the overall median life span of glioblastoma patients with 2.5 months. Although small, this was highly significant ($P < 0.001$) and the percent patients surviving at 30 months was ~25%, compared with 5% for patients who had not received temozolomide (5). This major advance has set a new standard for the treatment of patients with glioblastoma multiforme, against which other therapeutic approaches will now be measured. Among all chemotherapeutic agents available, platinum-derived drugs have played an important role in the treatment of solid tumors (6, 7), but their systemic administration has been limited by their toxicity. Carboplatin is a cisplatin analogue, which produces fewer side effects than cisplatin, but has a similar range of clinical activity (8). Hongo et al. have shown that carboplatin induces the same platinum-DNA adducts as cisplatin, although in vitro, it requires a 10-fold higher drug concentration and a 7.5-fold longer incubation time to produce an equivalent effect (8, 9).

The clinical effectiveness of carboplatin for the treatment of brain tumors is limited by the blood-brain barrier, which effectively reduces its uptake following systemic administration (10). Although the blood-brain barrier may be partially disrupted in some regions of the brain tumor, it is largely intact in more distant areas, thereby reducing the chemotherapeutic effectiveness in the surrounding normal brain in which there are infiltrating tumor cells. Strategies have been developed to improve drug delivery, such as the disruption of the blood-brain barrier or local administration of drug within the central nervous system by means of implantable pumps, biodegradable polymers, and convection-enhanced delivery (CED). CED has been used to enhance the distribution of drugs to brain tumors in a homogeneous and targeted manner (10–23). Its advantages over diffusion-dependent methods include greater volumes...
of distribution, more uniform drug concentrations within the treatment volume, and relative independence from molecular weight. It has been used experimentally by one of us (R.F.B.) to enhance the delivery of boronated anti–epidermal growth factor monoclonal antibodies for boron neutron capture therapy (24, 25).

Recently, we reported on the efficacy of synchrotron stereotactic radiotherapy (SSR) in combination with direct intratumoral (i.t.) injection of cisplatin [3 μg/5 μL of cis-diammine-dichloroplatinum (CDDP)] for the treatment of F98 glioma–bearing rats. This combined modality treatment resulted in survival times greater than 1 year in Fischer rats bearing F98 gliomas (26). Our initial hypothesis was that therapeutic efficacy was related to the production of Auger electrons and photoelectrons following irradiation of platinum atoms with beams of monochromatic X-rays tuned just above the Pt K-edge energy (Pt K-edge, 78.4 keV). Above this energy, extraction of electrons from the K-shell by the photoelectric effect results in the creation of K-shell vacancies. After removal of inner-shell electrons, the resulting vacancies are successively filled up by radiative and nonradiative transitions from outer-shell electrons whereby several low-energy photons and Auger electrons are released. The Auger electrons have short path lengths in tissue, producing high local energy deposition within a range of a few nanometers (27). The number of platinum atoms incorporated and their intranuclear position, therefore, determine the magnitude of cell killing (28).

The photoelectric cross section of Pt is 4.8× greater at 78.4 keV compared with 78.0 keV (2,860 and 593 barns/atom, respectively). Therefore, if the efficacy of treatment were related to emission of Auger electron, a greater therapeutic gain should be obtained following irradiation above rather than below the Pt K-edge. This enhancement has been observed by us in vitro at the molecular level. A larger number of double-strand breaks occurred when tumor cells were pretreated with cisplatin (CDDP) and subsequently irradiated above the Pt K-edge, compared with irradiation below the K-edge. Three times more double-strand breaks were measured with human SQ20B carcinoma cells pretreated with 30 μmol/L CDDP for 6 h (3 × 10^{10} atoms of platinum per cell; ref. 29) and 1.5× more double-strand breaks using F98 glioma cells (26). However, such an enhancement was not obtained in vitro, when the cells were pretreated with 3 μmol/L CDDP for 6 h, a treatment compatible with cell survival (cells survival rate, 25%; 4 × 10^6 atoms of Pt per cell; refs 29, 30). In vitro, the combined i.t. administration of CDDP (3 μg in 5 μL), followed 24 h later by 15-Gy irradiation, resulted in enhanced survival of F98 glioma–bearing rats, irrespective of whether the irradiation was done below or above the Pt K-edge (33% cure rate in both groups; ref 26).

Taken together, these findings suggested that therapeutic efficacy was not related to the emission of Auger electrons from the Pt atoms, when it was incorporated into tumor cells at therapeutic levels. This led us to postulate that the Pt-based chemoradiotherapy also could be carried out using high-energy X-rays from a linear accelerator. We hypothesized that local administration of carboplatin by CED in combination with photon irradiation would improve the survival of F98 glioma–bearing rats. In the present study, we first evaluated the toxicity and efficiency of intracerebral (i.c.) delivery of carboplatin by CED in syngeneic Fischer rats bearing F98 gliomas at varying carboplatin concentrations and dosing schedules. Based on these data, we then evaluated the efficacy of carboplatin, administered by CED, followed by fractionated radiation therapy using either 6-MV photons, produced by a linear accelerator or SSR with monochromatic 80-keV X-rays. Our data show the efficacy of this chemoradiotherapeutic approach using either radiation modality, and considerably broaden its clinical applicability because linear accelerators are widely available in radiation therapy departments throughout the world.

Materials and Methods

**F98 glioma model.** Following i.c. implantation into syngeneic Fischer rats, the F98 glioma forms a progressively growing, infiltrative tumor with characteristics similar to those of human high-grade gliomas, including a lack of response to a variety of therapeutic modalities (31, 32). Up until recently, the best survival data with this tumor model have been obtained using either boron neutron capture therapy (33) or, more recently, SSR in combination with direct i.t. injection of CDDP (26).

**Tumor implantation.** All operative procedures and animal care were carried out in conformity with the guidelines of the French Government (decree 87-848, 19th October 1987; licence nos. 7593 and A38071) and in accordance with the Laboratory Animal Care and Use Committee of the European Synchrotron Radiation Facility (ESRF). F98 glioma cells were routinely cultured as monolayers in DMEM (Life Technologies-Invitrogen-France) supplemented with 10% FCS, penicillin, and streptomycin. Male Fischer 344 rats (Charles River Laboratories), weighing 230 to 260 g, were anesthetized with an isoflurane inhalation technique followed by an i.p. injection of a mixture of ketamine (64.5 mg/kg of body weight) and xylazine (5.4 mg/kg of body weight). Additional i.p. injections of ketamine and xylazine were administered as needed to maintain anesthesia throughout the surgical procedures. The animals’ eyes were lubricated with an ocular lubricant. For therapy experiments, 10^5 F98 cells in 5 μL of serum-free DMEM were implanted i.c. into the right caudate nucleus (3.5 mm right to the bregma and 5.5 mm in depth). The syringe pump (model KDS 310, GENEX, Inc.; infusion rate, 2.5 μL/min) was directly mounted on the stereotactic frame (David Kopf Instruments) and the syringe (model 701 N, Hamilton) was attached to the pump. Before infusion using the same stereotactic coordinates, a 26-gauge needle was inserted to a depth of 6 mm and then withdrawn to a target depth of 5.5 mm from the skull surface. On completion of the infusion, the needle was left in place for 2 min and withdrawn slowly. The hole in the calvarium then was filled with bone wax and the operative field was cleaned with betadine before closure of the scalp incision.

**Chemotherapeutic drug delivery by CED.** Carboplatin was kindly supplied by the Grenoble University Hospital Pharmacy (MW, 371.25; Carboplatin Faulding 10 mg/mL, Pharmaceuticals S.A.). The carboplatin solution was diluted in isotonic NaCl solution to obtain the required concentrations for i.c. infusion. Thirteen days following tumor implantation, the rats were anesthetized as previously described. Carboplatin was administered by means of CED with the use of a syringe pump (model KDS 310, GENEX) at a rate of 0.5 μL/min (17). A 32-gauge needle, attached to a 50-μL syringe (model 1700, gas-tight, Hamilton), was placed in the tumor bed by using the same coordinates as those used for tumor implantation.

**Chemotherapy study.** The toxicity and/or efficacy of i.c. delivery of carboplatin by CED was evaluated in F98 glioma–bearing rats. Different infusion volumes (V_i), concentrations (c), and schedules of infusion relative to the time of tumor implantation were used. Animals were stratified as follows: group 1: controls (these animals received no treatment at all; n = 7); group 2: c = 1 mg/mL, V_i = 20 μL, 13 days (n = 10); group 3: c = 1 mg/mL, V_i = 40 μL, 13 days (n = 7); group 4:
c = 5 mg/mL, \( V_1 = 20 \mu L \), 13 days \((n = 6)\); group 5: \( c = 1 \) mg/mL, \( V_1 = 40 \mu L \), 8 days \((n = 8)\). Animals were weighed and monitored clinically. The side effects of carboplatin infusion were evaluated by determining loss of body weight and clinical status. Mean survival time (MST) and median survival time (MeST) were the end points of this study.

### Fractionated irradiations

SSR at 80 keV was carried out at the ESRF Medical Beamline and 6-MV irradiation was done at the Grenoble University Hospital. The X-ray dose was delivered over 3 days, with the first fraction given on day 14 after tumor implantation. In our previous studies (26, 34), the X-ray dose was delivered on day 14 in a single-fraction of 15 Gy at the tumor. The biologically equivalent dose/fractionation (BED) in a three-fraction regimen was calculated using the classic linear quadratic equation (35, 36):

\[
BED = nA \left[ 1 + d(x/b)^{-1} \right]
\]

where \( n \) is the number of fractions, \( d \) is the dose per fraction in Gy, and \( x \) and \( b \) are two variables that indicate the sensitivity of tumor or normal tissue to changes in dose fractionation. The \( x/b \) ratio is usually taken to be 10 for tumor and early-reacting tissues and 3 for late-reacting tissues like brain. The biologically effective dose (BED) for 15 Gy, delivered in a single fraction, using the \( x/b \) ratios indicated above, was 37.5 Gy in acute and tumor effects and 90 Gy in late effects (37). To obtain the same BED for tumor and early-reacting tissues, in a three-fraction regimen, the fraction size was determined by solving Eq. A using BED = 37.5 Gy and \( x/b = 10 \), which gave \( d = 7.3 \) Gy. Using the same equation for normal brain and late-responding tissues (BED = 90 Gy and \( x/b = 3 \)), the fraction size \( d \) was 8.1 Gy, given in three fractions. Based on these evaluations, we chose to deliver the radiation dose in three fractions with 8 Gy per fraction to be biologically comparable to a single 15-Gy fraction previously used in our preclinical studies (26, 34).

### Stereotactic synchrotron radiation

Anesthetized animals were irradiated as previously described (26, 34). Briefly, the irradiations were done with monochromatic radiation from the ESRF ID17 beamline (38), which was tuned at 80 keV (80-eV energy bandwidth). The right hemisphere was centered on the rotation axis of the irradiation system and the beam was shaped by tungsten slits to 10 mm in width and 1 mm in height. The dose was delivered while the rat was being rotated, and translating upwards between each of the 13 adjacent 360-degree arcs so that the irradiated target volume encompassed a 10 mm in diameter and 13 mm in height cylinder. A GafChromic film (MD-55, International Specialty Products) was exposed during the rats’ irradiation at the ESRF.

### Chemoradiotherapy experimental groups

Chemotherapy was initiated 13 days following stereotactic implantation of 10^6 F98 glioma cells and X-ray irradiations were started 24 h later. The animals received a dose of carboplatin (concentration, 1 mg/mL; \( V_1 = 20 \mu L \)), which was moderately toxic when administered alone. The animals were randomized into six experimental groups of 6 to 12 animals each. For those experiments carried out at the University Hospital (6-MV linear accelerator irradiation), the groups were stratified as follows: group 6, untreated controls \((n = 9)\); group 2, chemotherapy controls, which received carboplatin (20 \( \mu \)g in 20 \( \mu \)L by CED; \( n = 10)\); group 7, irradiated controls at 6 MV \((n = 11)\); and group 8, carboplatin (20 \( \mu \)g in 20 \( \mu \)L administered by CED), followed by three 8-Gy fractions (6 MV) administered over 3 days \((n = 12)\). For those experiments carried out at the ESRF (80 keV), the groups were stratified as follows: group 9, untreated controls \((n = 6)\); group 10, irradiated controls at 80 keV \((n = 11)\); and group 11, carboplatin (20 \( \mu \)g in 20 \( \mu \)L administered by CED), followed by three 8-Gy fractions at 80 keV over 3 days \((n = 12)\).

### Monitoring of clinical status and neuropathologic evaluation

After therapy, the animals were weighed thrice a week and their clinical status was monitored. The combination of sustained weight loss, ataxia, and periorbital hemorrhage has been shown to be indicative of progressively growing tumors (40). In such cases, the animals were euthanized by an intracardiac injection of Dolethal (150 mg/kg, Vetoquinol) and survival times were determined by adding 1 day to the time between tumor implantation and euthanasia. The long-term survivors were defined as rats living >200 days and the surviving animals were euthanized at this time point. Following euthanization, the brains of selected animals in the therapy studies were removed, fixed in 10% buffered formalin, and then cut coronally at the level of the optic chiasm and 2 mm anterior and posterior to it. Coronal slices were embedded in paraffin, cut at 4 \( \mu m \), stained with H&E, and then examined microscopically to assess histopathologic changes.

### Statistical evaluation of survival data

Kaplan-Meier survival curves were plotted for each group. Differences between various treatment groups were assessed for statistical significance by means of the log-rank test (IMP, SAS Institute, Inc.). Those rats still alive at 200 days after tumor cell implantation were euthanized. Minimal statistical significance was defined at \( P < 0.05 \). The MST, SE, and MeST were calculated with a value of 200 days for the rats still alive at the end of the study. When the last observations in each group are the only ones censored, then the estimate of the mean is approximately the arithmetic mean of the survival times with the last censoring observations included in the

### Table 1. Rat weight loss percentage 7 d after chemotherapy treatment of F98 glioma

<table>
<thead>
<tr>
<th>Group</th>
<th>Infusion volume (( \mu L ))</th>
<th>Carboplatin concentration (mg/mL)</th>
<th>Delivery time (d)</th>
<th>N*</th>
<th>No. death</th>
<th>&lt;5%</th>
<th>6-10%</th>
<th>11-30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20</td>
<td>1</td>
<td>13</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>0</td>
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<tr>
<td>3</td>
<td>40</td>
<td>1</td>
<td>13</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>5</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>1</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE: The table indicates the number of animal that died within 7 d after chemotherapy treatment, and the number of animals that lost weight, comparatively to their initial weight. The weight lost was classified in various ranges (<5%, 6-10%, and 11-30%). *N* is the number of animals per group.
One animal that received carboplatin at a dose of 40 g/20 mL delivered on day 13 after tumor implantation (○), CED of carboplatin 20 g/20 mL delivered on day 13 after tumor implantation (□), and CED of carboplatin 100 g/20 mL delivered on day 13 after tumor implantation (△). One animal that received carboplatin at a dose of 40 g/40 mL, on day 8 after tumor implantation, was still alive at day 200.

Fig. 1. Kaplan–Meier survival plots for F98 glioma–bearing rats after carboplatin chemotherapy. Survival times in days after tumor implantation have been plotted for untreated animals (○), CED of carboplatin 40 μg/40 μL delivered on day 13 after tumor implantation (□) or on day 8 after tumor implantation (△), and CED of carboplatin 20 μg/20 μL delivered on day 13 after tumor implantation (○). There were no early deaths. In group 2, which received 20 μg/20 μL, there were no early deaths. Conversely, the weight lost was mild (<10% of body weight) in group 2, which received 20 μg/20 μL on day 13. The survival of rats in this group was significantly different from that of the untreated control group (P < 0.0001). The log-rank test was not used for the other groups because the survival plots crossed each other due to early deaths. In such instances, the log-rank test is unlikely to detect differences between groups (41). In group 5 that received chemotherapy 8 days after tumor implantation, the rats had a small loss in weight (<5%), and no early death was observed. It is noteworthy that one rat was still alive at the end of the study (200 days).

Therapeutic response following chemoradiotherapy. For the chemoradiotherapy study, 20 μg/20 μL of carboplatin was administered by CED at a rate of 0.5 μL/min, 13 days after implantation of 10^3 F98 glioma cells, and radiotherapy was initiated 24 h later. Survival data are summarized in Table 3 and Kaplan-Meier survival plots are shown in Fig. 2. The untreated rats had a MeST of 28 days and a MST of 28 ± 1 days (range, 26-32 days) compared with a MeST of 51 days and a MST of 52 ± 2 days (range, 42-65 days) for the irradiated controls at 80 keV (P < 0.0001). Similarly, the 6-MV, photon-irradiated controls had a modest increase in MeST to 42 days and a MST of 43 ± 2 days (range, 35-56 days) compared with a MeST of 28 days and a MST of 29 ± 1 days for the untreated rats (P < 0.0001). Animals bearing F98 gliomas, which had received carboplatin (dose = 20 μg/20 μL) by CED, had a MeST of 45 days and a MST of 55 ± 8 days with one rat surviving 120 days, which was significantly different from the untreated control group (P < 0.0001). The corresponding %ILS relative to the median were 63%, 82%, and 50% for chemotherapy alone and irradiation alone at 80 keV or 6 MV, respectively. The combination of carboplatin and irradiation resulted in the greatest prolongation in survival time. Animals that received chemotherapy followed by SSR at 80 keV had a MeST of 60 days and a MST of 51 ± 16 days (censored; range, 47-200* days). Animals that received chemotherapy, followed by irradiation with 6-MV photons, had a MeST of 79 days and a MST of 97 ± 15 days (censored; range, 50-200* days). Most significantly, there was a cure rate of 16.6% for animals that received carboplatin followed by fractionated, 6-MV photon irradiation, with a 182% ILS of the MeST compared with that of untreated controls. There were also long-term survivors and/or cured animals in the chemoradiotherapy group irradiated at 80 keV. One rat was still alive at 200 days and another died at day 198. Survival of the animals that received chemoradiotherapy was significantly different from those of the irradiated controls that received either 6-MV (P < 0.0001) or 80-keV photons (P = 0.041). Although the MST and MeST

Results

Chemotherapy study in rats bearing glioma. All animals that received i.t. carboplatin by CED lost weight within 7 days after treatment. Three of seven rats that received 40 μg/40 μL carboplatin by CED at day 13 lost >10% of their body weight (Table 1), and one rat in that group died early on day 16 (Fig. 1; Table 2). One early death (day 16) also was observed in chemotherapy group 4 that received 100 μg/20 μL of carboplatin at day 13. Conversely, the weight lost was mild (<10% of body weight) in group 2, which received 20 μg/20 μL on day 13. The survival of rats in this group was significantly different from that of the untreated control group (P < 0.0001). The %ILS was determined relative to MST or MeST of untreated controls as follows:

\[
\text{% ILS} = \frac{\text{MST} - \text{MST}_{\text{Control}}}{\text{MST}_{\text{Control}}} \times 100
\]

<table>
<thead>
<tr>
<th>Group</th>
<th>N*</th>
<th>Carboplatin CED treatment (dose/volume)</th>
<th>Survival time (d)</th>
<th>% Increased life span</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>Untreated</td>
<td>22-34</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20 μg/20 μL</td>
<td>32-120</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>40 μg/40 μL</td>
<td>16-59</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>100 μg/20 μL</td>
<td>16-52</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>40 μg/40 μL (at day 8)</td>
<td>27-200*</td>
<td>120</td>
</tr>
</tbody>
</table>

NOTE: Carboplatin was delivered by CED on day 13 after tumor implantation for groups 2, 3, and 4, and on day 8 for group 5. A survival time of 200 d was considered as the end point of the study. Rats still alive at 200 d after inoculation of 10^3 F98 glioma cells were euthanized.

* N is the number of animals per group.

† One rat was still alive at day 200.
of the chemoradiotherapy groups were greater than those of the chemotherapy alone group, the differences were statistically significant only for chemoradiotherapy group irradiated with 6-MV photons (P = 0.004) and not with 80-keV X-rays (P = 0.176). Most importantly, the survival times of the two chemoradiotherapy groups (6-MV and 80-keV X-rays) were not significantly different from each other (P = 0.173).

**Histopathologic studies.** Microscopic examination of the brains of three rats, which had received carboplatin and 6-MV (2 rats) or 80 keV (1 rat) photons and were euthanized on day 200, revealed no evidence of tumor. One animal that had received 80-keV X-rays and died at day 198 also had no evidence of residual tumor. The brains of two animals that received carboplatin alone were also examined. One, which received 100 μg/20 μL on day 13 after tumor implantation and died on day 16, showed a small focus of necrotic tumor cells, rarefaction of white matter, and microfoci of hemorrhage. These findings suggest that this was a therapy-related death. The other one, which received 40 μg/40 μL on day 8 after tumor implantation, was still alive at termination of the study (day 200) and showed no evidence of tumor.

### Discussion

The major finding in the present study was that carboplatin, administered by CED in combination with external beam X-irradiation, resulted in a significant enhancement in MST, and the cure of a subset of F98 glioma–bearing rats was independent of the X-ray beam energy. Rats that received chemotherapy, followed by 6-MV X-irradiation, had a MeST of 79 days, a corresponding 182% ILS (MeST), and a cure rate of 16.6% at 200 days. The chemoradiotherapy group irradiated at 80 keV had a MeST of 60 days (114% ILS) with one long-term survivor (one rat died at day 198) and one cured animal (8.3%). Using the same experimental tumor model, one of us (R.F.B.) has obtained a 25% cure rate following boron neutron capture therapy (33). In a previous study (26), we reported a 33% cure rate of F98 glioma–bearing rats after i.t. injection of cisplatin (3 μg/5 μL) in combination with 15 Gy of synchrotron radiation. In that study, animals that received chemoradiotherapy had a MeST of 214 and 194 days at 78.0 and 78.8 keV, respectively, in the first experiment, and 131 and 91 days in the second, which was carried out 4 months later under the same conditions. The survival of the animals irradiated with an X-ray beam tuned above the Pt K-edge was not statistically different compared with irradiation below the K-edge. In both cases, 33% of the treated rats were still alive 1 year later. In the same way, using nontoxic cisplatin concentrations, we have not observed any significant in vitro difference in the survival of SQ20B cells when irradiated either above or below the Pt K-edge (30).

The results obtained in the present study confirm our initial findings, but suggest an alternative explanation relating to the role of DNA damage induced by atomic inner-shell relaxation, following a photoelectric event. If the efficacy of chemoradiotherapy was primarily related to inner-shell ionizations of

<table>
<thead>
<tr>
<th>Irradiation energy</th>
<th>Treatment</th>
<th>N*</th>
<th>Survival time (d)</th>
<th>% Increased life span</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td>Mean ± SE</td>
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<td>6 MV</td>
<td>Untreated controls</td>
<td>9</td>
<td>25-36</td>
<td>29 ± 1</td>
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<td></td>
<td>Chemotherapy controls</td>
<td>10</td>
<td>32-120</td>
<td>55 ± 8</td>
</tr>
<tr>
<td></td>
<td>Irradiated controls</td>
<td>11</td>
<td>35-56</td>
<td>43 ± 2</td>
</tr>
<tr>
<td></td>
<td>Chemoradiotherapy</td>
<td>12</td>
<td>50-200†</td>
<td>97 ± 15</td>
</tr>
<tr>
<td>80 keV</td>
<td>Untreated</td>
<td>6</td>
<td>26-32</td>
<td>28 ± 1</td>
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<td>Irradiated controls</td>
<td>11</td>
<td>42-65</td>
<td>52 ± 2</td>
</tr>
<tr>
<td></td>
<td>Chemoradiotherapy</td>
<td>12</td>
<td>47-200†</td>
<td>81 ± 16</td>
</tr>
</tbody>
</table>

NOTE: Carboplatin (20 μg/20 μL) was injected by CED on day 13 after tumor implantation and was followed by radiotherapy (three fractions of 8 Gy), delivered on days 14, 15, and 16 after inoculation of 10³ F98 glioma cells. A survival time of 200 d was considered as the end point of the study. Rats still alive at 200 d were euthanized.

* N is the number of animals per group.
† Rats still alive after 200 d were euthanized at this date.
§ The number in parentheses indicates the number of rats surviving >200 d.
Pt atoms and subsequent Auger electrons cascades, synchrotron radiation, tuned above the Pt K-edge, should have been much more effective than the same treatment with 6-MV photons from a linear accelerator. Bernhardt et al. (27) have studied the role of atomic inner-shell ionization and subsequent relaxation of platinum, and the resulting DNA damage. It was observed that the amount of energy deposited in a local area surrounding the site of absorption was quite small, even when as many as $10^3$ Pt atoms were intercalated with DNA. Although the photoelectric cross section for inner-shell ionizations of Pt atoms is relatively large ($2.91 \times 10^3$ barns/atom at 78.39 keV), K-shell ionization events occur quite rarely because only a small number of Pt atoms per base pair can be tolerated in vivo. Our results suggest that the therapeutic gain obtained with i.t. injection of either cisplatin or carboplatin followed by X-irradiation was not predominantly due to Auger electrons emitted from the Pt atoms, but rather involved other mechanisms (27). However, these findings do not refute the premise on which SSR is based: the irradiation of high Z number atoms with energies the same as those of K-shell electrons.

Carboplatin, by itself, is an active cytoreductive chemotherapeutic agent (42). In the present study, animals that received carboplatin at a dose of 20 g/20 L had a MeST of 45 days (median %ILS, 63%), and there was one long-term survivor (120 days) with no early deaths. The highest doses of carboplatin tested (40 g/40 L and 100 g/20 L) were toxic, as evidenced by significant weight loss of F98 glioma–bearing rats within the first week after drug administration, which strongly suggests that this was drug related. However, it is noteworthy that one rat that received 40 g/40 L of carboplatin 8 days after tumor implantation was still alive at the end of the study (200 days). Intracerebral administration of carboplatin has been evaluated for the treatment of glioma–bearing rats in several other studies (10, 43–45). Degen et al. (10) have shown that carboplatin delivered by CED was effective in the treatment of 9L gliosarcoma–bearing rats. In their study, among the rats that received carboplatin (40 g/40 L) on day 7, three of four animals survived to 120 days, at which time the study was terminated. There was one early death at day 19. In the same study, the toxicity of carboplatin, delivered by CED, into the striatum of non–tumor-bearing rats was not studied, but rather involved other mechanisms (27). However, these findings do not refute the premise on which SSR is based: the irradiation of high Z number atoms with energies the same as those of K-shell electrons.

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In conclusion, our data show the therapeutic efficacy of i.c. administration of carboplatin by means of CED in combination with fractionated radiotherapy in F98 glioma–bearing rats. Chemotherapy by itself improved the survival of F98 glioma–bearing rats, but this was enhanced by the addition of external beam photon irradiation. It remains to be determined if this effect was additive or synergistic. Our data show that high-energy X-ray irradiation (6 MV) was as effective as synchrotron X-ray irradiation for treatment of the F98 glioma. This significantly broadens the applicability of this chemotherapeutic approach for the treatment of patients with high-grade malignant brain tumors because it could be more easily translated into a clinical trial using 6-MV photons instead of synchrotron-derived X-rays.

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6 Similar survival data recently have been obtained by Drs. Rolf Barth and Weilian Yang that are confirmatory of those reported in this article. F98 glioma–bearing rats treated with either cisplatin alone, administered by convection enhanced delivery, or in combination with LINAC irradiation with 6-MV photons, had mean and median survival times of 73 and 71 days, respectively, compared with 21 days for untreated and 28 days for irradiated control animals.

References


Enhanced Survival and Cure of F98 Glioma–Bearing Rats following Intracerebral Delivery of Carboplatin in Combination with Photon Irradiation

Julia Rousseau, Caroline Boudou, Rolf F. Barth, et al.


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