Combined Radiotherapy and Razoxane in the Treatment of Chondrosarcomas and Chordomas

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Abstract. Background: Chondrosarcomas and chordomas are reported to have low radio-sensitivity. Therefore, a study was undertaken to explore the radioresponsiveness of these tumours using the sensitising agent razoxane. Patients and Methods: Thirteen chondrosarcomas and five chordomas were irradiated with high-energy photons and razoxane in the period from 1984 to 2003. The median tumour dose was 60 Gy in the chondrosarcomas and 63 Gy in chordomas. Razoxane tablets were given at a dose of 125 mg twice daily starting 5 days before the first irradiation. The drug was continued on radiation days. Results: Eight out of the 13 chondrosarcomas had unresectable or recurrent measurable disease. There were one complete and five partial responses, while two tumours remained unchanged (response rate 75%). The median duration of response was 22 months. Three out of four patients without clear surgical margins and one patient with clear margins had locally controlled disease. Overall, local control was achieved in seven out of twelve patients who were not radically resected. All five patients with chordomas survived 5 years and remained locally controlled at that time. Among four measurable tumours, two complete and one partial regression were noted. Razoxane was well tolerated; the dose limiting toxicity was leukopenia. Conclusion: Photon irradiation together with razoxane induces major responses in a majority of patients with chondrosarcomas and chordomas. This combination therapy seems to be more effective than photon irradiation alone.

A complete surgical resection is the ultimate goal in the treatment of chondrosarcomas (CS), but sometimes gross residual disease remains or the primary tumour is unresectable. Chondrosarcomas are regarded as tumours with a low sensitivity to radiation treatment (1-3). However, the local control rates after radiotherapy are different and depend on the tumour grade and the sites of origin of the primary tumour. High local control rates were achieved in chondrosarcomas of the head and neck region (4-7), whereas tumours of the chest or the pelvic area were associated with a worse prognosis (1, 9).

An incomplete resection is to be expected even more frequently in chordomas. Using photon irradiation alone, the long-term local control rate was approximately 25 to 30% (2). Only with high LET irradiation (neutrons, protons or heavy ions) were better results achieved (10-12). High LET irradiation, however, is expensive and not easily available everywhere. Therefore, the search for new treatment modalities seems appropriate.

The piperazine derivative razoxane (ICRF 159) was first successfully applied together with radiotherapy in soft tissue sarcomas. In 1979, it was indicated by Ryall et al. as an effective sensitizer in CS as well (13). Razoxane can be given orally. The drug is excreted by the kidneys and its serum half-life is 3.5 h (14). It was reported to have pronounced radiosensitizing abilities in animal experiments and clinical trials (15-17). There is proof of several modes of action (14, 18-22): a. Razoxane blocks the cell cycle in the G2/M-phase (the most radiosensitive phase); b. It normalises pathological tumour blood vessels; c. It is anti-invasive for tumour cells at the level of the basal membrane; d. It inhibits the topoisomerase II; e. It slows down the tumour growth in animal models.

Patients and Methods

The study included patients with a confirmed histology of a chondrosarcoma (CS) or chordoma, referred for postoperative or palliative radiotherapy from 1984 to 2003. There were 13 patients with CS and five patients with chordomas who received radiation treatment together with razoxane according to the protocol of Ryall et al. (13).

The main pretreatment characteristics of the patients with CS are shown in Table I. Secondary CS associated with Maffucci-Syndrome or other congenital diseases were not found in this series. One patient had a history of enchondromas, while another reported exostoses prior to diagnosis.
The initial diagnostic work-up was done by CT scans and/or MRI. Lung metastases were detected or excluded by chest X-rays and/or CT scans of the thorax. Laboratory analyses included a complete blood count, nitrosoarone, creatinine, serum calcium, alkaline phosphatase, lactate dehydrogenase and total protein in the serum.

Radiotherapy. The radiation treatment was performed with high-energy photons (6 and 25 MeV). As a rule, multiple fields based on CT treatment planning were used. Daily fractions of 200 cGy were applied five times a week. The median tumour dose in CS was 60 Gy (range, 54-65 Gy) and 63 Gy (range, 54-67 Gy) in chordomas.

Razofoxane. Razofoxane was concomitantly given during the radiation treatment. The medication was started 4 to 5 days before the first irradiation and then continued on the radiation days. The daily dose was 2 x 125 mg razofoxane given orally. During the radiotherapy, the first tablet was taken 1 h before the irradiation and the rest of the dose in the evenings. The drug intake was interrupted on weekends. The median total dose of razofoxane was 8.5 g (range, 6-15 g) in chondrosarcomas and 7.6 g (range, 5.4-11.5 g) in chordomas. The dose range may be explained by the variable onset of leukopenia or other side-effects.

Definition of response. Response was defined according to earlier standard criteria, not by RECIST. A complete remission at the site of irradiation is defined as a total disappearance of the tumour as ascertained by clinical means and imaging procedures. A complete restoration of the bony fine structure in X-rays was not a prerequisite. A partial response meant a reduction of the initial tumour size of at least 50%. A tumour was regarded as changed if the alteration of volumes were approximately +/- 25%. Local tumour control was defined as no regrowth at the site of irradiation as long as the patient survived.

Follow-up. All patients were followed-up until October 2005 or until their death. The median follow-up time of the living patients with CS was 54 months (range, 28 to 160). The patients with chordomas had a minimum follow-up of 78 months.

Results

Chondrosarcomas. All the relevant data on pretreatment characteristics, treatment details and the outcome of the 13 patients with CS receiving razofoxane are listed in Table I. Eight patients had unresectable, measurable primary tumours or recurrences, five patients received postoperative radiotherapy (one after a R-0 resection, four after R-1 resections).

Among the eight patients with measurable disease (# 6 to # 13 in the Table), there were one complete and five partial responses and two tumours did not change, corresponding to an objective response rate of 75%. The median duration of response was 22 months (range 15-90). Disease in four out of the eight patients remained locally controlled, including in one woman who underwent a secondary amputation of her knee. Although in partial remission, she had functional impairment of her knee joint. The recurrent tumour progressed even

Chordomas. All five patients survived 5 years and the disease remained locally controlled during that time. The median survival is 100 months (range, 78 - 204+ months). One patient died from cardiac insufficiency with a persistent sacral chordoma after 8 years, another died after 6.5 years from bleeding after surgery for local recurrence at the thoracic spine. Recently, a third patient died from distant metastases after 8.4 years, the primary having been controlled. The disease remained locally controlled for 5, 8.4, 6.4, 15+ and 17+ years. Two patients are alive with no evidence of disease. Among the four patients with measurable disease, there were two complete responses (CR), one partial response (PR) and one with no change (NC).

As to acute toxicity, mucosal reactions were the most frequent. Two out of five patients had WHO grade 3 leukopenia due to razofoxane. Neurological late reactions, e.g., lesions of the brain stem or optic nerve damage, were not observed.

Discussion

Relatively few results regarding the radioresponse of CS are available in the literature. The tumours are frequently regarded as resistant to irradiation, but most authors do not give any response rates or other detailed descriptions. However, some authors have reported higher local control rates for incompletely resected CS, not only in the head and neck area (7), but also at the spine or pelvic bones (23). The authors assume false resistance to irradiation due to a tendency of these tumours to regress slowly and the persistence of skeletal destruction often seen in X-rays after radiation therapy. In addition, in earlier investigations rather low radiation doses were applied (23).

More details concerning the radioresponsiveness of CS are found in studies comparing photon irradiation and neutrons. Laramore et al. reported an objective response rate of 33% with conventional photon irradiation versus 49% with neutrons (24). In an analysis by McNaney et al. (25), only one of seven patients remained locally controlled when photon radiotherapy alone was used. In this connection, it should be noted that two of our own patients, one with microscopic residuals and another with recurrent tumour measuring 8x8 cm, had been treated with radiotherapy alone in an earlier randomized study. The recurrent tumour progressed even
during the radiation therapy. The two patients survived 7 and 9 months. They had the shortest survival times of all our patients with CS.

CS are also regarded as being insensitive to cytotoxic agents given either with or without radiotherapy. The only report of an increase of the rate of radioresponses by the addition of chemical agents came from Ryall et al. (13). The authors combined razoxane with radiotherapy and achieved a rate of 62.5% CR and PR. We observed similar results, i.e., a 75% response rate, but the occurrence of a CR in measurable tumours was less frequent compared to that reported in the investigation by Ryall et al. Thus, major responses over many months can be achieved in the majority of unresectable CS through the combination of radiotherapy and razoxane.

The site of origin of CS is an important prognostic factor and criterion in the assessment of therapeutic results. For instance, CS of the skull base irradiated by heavy ions offers favourable local control and outcome (4, 10). Likewise, CS of the larynx are to be seen as a separate

<table>
<thead>
<tr>
<th>Pat. #</th>
<th>Age</th>
<th>Gender</th>
<th>Primary site</th>
<th>Stage; Grade</th>
<th>Situation before radiotherapy</th>
<th>RTx Gy/fract/dose (g)</th>
<th>Razoxane Effect of RTx</th>
<th>Treatment results</th>
<th>Local control</th>
<th>Survival (months)</th>
<th>Remarks; causes of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>Right thigh</td>
<td>T1N0M0; G2</td>
<td>R-0 resection adjuvant radiation therapy</td>
<td>60/30/11, 6 n.m. yes</td>
<td>87+</td>
<td>NED; end of follow up after 87 m</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>Left thigh</td>
<td>T2N0M0; G2</td>
<td>R-1 resection</td>
<td>60/30/08, 9 n.m. yes</td>
<td>160+</td>
<td>NED; chronic edema of lower leg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>Fourth rib</td>
<td>T2N0M0; G2 left side</td>
<td>R-1 resection</td>
<td>60/30/6, 9 n.m. no</td>
<td>55</td>
<td>Regrowth after 28 months at field border, further surgery + RTx; died of lung metastases</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>48</td>
<td>M</td>
<td>Sternum</td>
<td>T2N0M0; G4 12x8 cm</td>
<td>R-1 resection</td>
<td>59/32/6, 8.5 n.m. yes</td>
<td>12</td>
<td>Died of lung metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>M</td>
<td>Ethmoid bone</td>
<td>T2N0M0; G4</td>
<td>R-1 resection</td>
<td>60/30/06, 7.5 n.m. yes</td>
<td>42+</td>
<td>NED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>F</td>
<td>Orbital, left</td>
<td>T2N0M0; G4</td>
<td>Second recurrence after surgery (size 0.8 x 0.8 cm)</td>
<td>56/28/06, 8.75 CR no</td>
<td>56+</td>
<td>Local regrowth after 48 months, salvage surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>F</td>
<td>Second rib, left side</td>
<td>T2N0M0; G2</td>
<td>Mediastinal mass (8 x 8 cm), 8 years after diagnosis</td>
<td>65/27/11, 15.25 NC yes+</td>
<td>22</td>
<td>*last follow-up after 17 months, cause of death unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>Sternum</td>
<td>T2N0M0; G1</td>
<td>Third recurrence and regional mets, size 1-3cm, respectively</td>
<td>65/33/6, 7 NC no</td>
<td>52+</td>
<td>Local regrowth after 21 months, further surgery; alive with disease</td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>74</td>
<td>F</td>
<td>Groin</td>
<td>T2N0M0; G3</td>
<td>Unresectable; biopsy only; size 17x11 cm (1800 ml)</td>
<td>60/33/08, 6.5 PR yes</td>
<td>22</td>
<td>Died of lung metastases</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>80</td>
<td>F</td>
<td>Knee, left</td>
<td>T2N0M0; G2</td>
<td>Unresectable; biopsy only; size 5 x 5 cm</td>
<td>54/27/06, 8 PR yes *</td>
<td>90</td>
<td>*Secondary amputation because of instability of knee; intercurre. death</td>
<td></td>
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<td></td>
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<tr>
<td>11</td>
<td>58</td>
<td>M</td>
<td>Larynx</td>
<td>T2N0M0; G2</td>
<td>Primary tumor, size 5 x 5 cm; biopsy only; surgery refused</td>
<td>62/33/08, 9.25 PR yes</td>
<td>85</td>
<td>Died intercurrently (cardiac insufficiency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>81</td>
<td>M</td>
<td>Upper arm, right side</td>
<td>T2N1M1; G2 M1=chest wall</td>
<td>First recurrence at upper arm, axilla, chest wall (extensive)</td>
<td>60/30/6, 8.5 PR no</td>
<td>28+</td>
<td>Local regrowth after 15 months, lung metastases after 27 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>Os ileum, right side</td>
<td>T2N0M0; G1</td>
<td>Unresectable; biopsy only; size 20 x 15 cm</td>
<td>60/30/12, 11.75 PR no</td>
<td>38</td>
<td>Local regrowth after 20 months, died from local recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M = male; F = female; CR = complete remission; NC = no change of tumor size; PR = partial response; n.m. = not measurable ; RTx = radiotherapy; NED = no evidence of disease; + patient alive.
group with a better prognosis (6, 7). In our patient series, there were no CS of the base of the skull, but three tumours in other parts of the head and neck, e.g., larynx, orbita and paranasal sinus.

In chordomas, a conventional treatment with photon irradiation of 50 Gy leads to local control rates from 25 to 30% (2). In patients with residual disease, the median time-to-recurrence or metastasis is 3.5 years (2, 26, 27) and in some reports even less (28, 29). Therefore, several authors came to the conclusion that inoperable or gross residual chordomas can rarely be cured by conventional photon irradiation (8, 26, 28, 30).

With extensive surgical procedures (31) and high LET irradiation, it was possible to increase the local control rate to 60-65% (11, 12). There are, however, few facilities offering high LET irradiation, which involve higher costs and possible serious side-effects at the brain stem, chiasma opticum or the hypophysis (2, 10). Improvement of the local control of chordomas was also claimed the use of modern 3D planning and radiosurgery with photons (32) but the follow-up time in these patients is still short.

The local tumour control over 5 years in all of our five patients and objective tumour responses in three out of four measurable lesions compare favourably with the available literature. It seems to be a result that deserves further study. For instance, in a recent series of 18 patients with skull base chordomas treated with spot scanning proton beam therapy, no complete or major (>50%) response was observed (33). Of course, the small number of cases does not allow far reaching conclusions, but the patients were not selected and had a considerable follow-up time. The more favourable chondroid variant could be excluded in all but one patient in a secondary review by the pathologist (S.D.). The treatment is well tolerated and easy to perform in every radiotherapy department.

Taken together, the combination of radiotherapy and razoxane increases the rate of objective responses in CS and chordomas compared to radiotherapy alone. The earlier results of Ryall et al. (13), using radiotherapy combined with razoxane for CS, were confirmed in this patient series. This treatment could be a valid alternative or even an adjunct to high LET irradiation with protons or heavy ions.

Razoxane is a largely neglected radiosensitizer, although it has an interesting spectrum of modes of action and showed impressive clinical results. Unfortunately, since 2004 razoxane has been discontinued by Cambridge Laboratories (UK) because it has not come into standard praxis as yet and had, therefore, a limited use. The question under debate is whether dexrazoxane (ICRF 187, Cardioxane®, Zinecard®) should be used instead of the razoxane tablets. Dexrazoxane is the more soluble (+) enantiomorph of the racemic mixture known as ICRF 159, or razoxane. The drug must be given intravenously. To date, there is limited clinical experience in giving dexrazoxane in combination with radiotherapy, but preclinical studies have already indicated that the drug may also show synergism with radiotherapy (34).

References


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