Razoxane and Vindesine in Advanced Soft Tissue Sarcomas: Impact on Metastasis, Survival and Radiation Response

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Abstract. *Background: The treatment options in advanced soft tissue sarcomas (STS) are limited. In a pilot study, an anti-metastatic and radiosensitizing treatment concept was explored. Patients and Methods: Twenty-one patients with unresectable and/or oligometastatic STS received the drugs razoxane and vindesine supported by radiotherapy and surgery. Long-term treatment was intended in metastatic disease. Forty-one patients with comparable stages of STS treated with contemporary chemotherapy served as non-randomised controls. The prognostic parameters of the groups were comparable. Results: In the study group, the median number of new metastases after 6 months was 0 (range, 0-40) and after 9 months likewise 0 (0-70). The corresponding numbers in the control group were 4.5 (range, 0-40) and 9 (0->100) ($p<0.001$). The progression-free survival at 6 months was 71% in the study group and 23% in the controls, and the median survival time from the occurrence of the first metastasis was 16 months versus 9 months. The rate of major responses under radiotherapy combined with razoxane and vindesine was 88%, and in the control group 62% ($p=0.007$). The combined treatment was associated with a low to moderate toxicity. Conclusion: The treatment combination inhibited the development of remote metastases in the majority of patients with STS and prolonged survival to some extent.*

Available treatment options for unresectable and disseminated soft-tissue sarcomas (STS) are limited. Although some progress has been made in controlling inoperable or gross residual STS by neutron irradiation (1), isolated limb perfusion with biologically active agents and melphalan (2), or combinations of irradiation with radiosensitising agents such as bromodesoxyuridine and iododesoxyuridine (3) or razoxane (4, 5), distant metastases remain an obstacle to prolonged survival. From this background, an attempt to extend a merely radiosensitizing therapy with razoxane by the addition of an antiinvasive drug appeared worthwile.

Desacetyl-vinblastine-amide (Vindesine, (VDS)) is a semisynthetic vinca alkaloid. It was shown to be effective in cytotoxic combination therapies in soft tissue sarcomas (6) and to have putative radiopotentiating abilities (7, 8). In addition, VDS is a microtubule inhibitor with pronounced anti-invasive effects *in vitro* (9, 10) and proven anti-metastatic activity in animal systems (11, 12).

The radiosensitizer (4, 5, 13) razoxane is an inhibitor of topoisomerase II (14). This drug is of particular interest in the treatment of STS because of its potential to normalize pathological tumour blood vessels (15-17) and due to its anti-invasive effects (18). The drug has been shown to slow the growth rate of transplanted tumours (16) and to completely suppress the development of distant lung metastases in animals (15, 17, 19).

We therefore aimed at investigating the impact of the razoxane/VDS combination therapy on the dynamics of metastasis, on survival and on the radiation response in patients undergoing radiotherapy for advanced soft tissue sarcomas (STS).

Patients and Methods

In a prospective study from 1996 to 2004, 21 patients with advanced adult-type STS received a combined treatment with razoxane and VDS supported by radiotherapy and, in some instances, by surgery. From these patients, 7 had unresectable primary tumours or recurrences without metastases at baseline and 14 had early metastatic disease, *i.e.* less than 7 distant metastases. Forty-one patients with comparable age, disease-stages and prognostic features served as non-randomized, retrospective controls. The performance of the study was in accordance with the ethical standards of the Helsinki Declaration.

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The anti-metastatic approach. Conventional cytotoxic chemotherapy is applied to induce disease regression or stable disease. In cases of progressive disease, the treatment is usually judged as not effective and will be changed or terminated. In contrast, the antimetastatic approach has the intention of preventing further metastasis – irrespective of the achievement of an objective response of existing lesions. This approach was pursued in our cohort of patients on combined razoxane/VDS treatment: If pre-existing metastases proved resistant to the combination of razoxane/VDS, this therapy was continued ('treatment beyond progression'). In addition, the respective lesions were irradiated and in some cases removed by surgery. In case of few new metastases, the razoxane/VDS treatment was also continued and local treatment measures were performed again. However, the combination therapy was regarded as ineffective and terminated if more than 5 new metastases appeared within 3 months.

Drug treatment. The study patients received a metronomic chemotherapy with razoxane tablets and small doses of VDS together with concurrent radiotherapy. The treatment was terminated on complete response of unresectable tumours but continued if metastases were present at the time of patient referral. The protocol required razoxane (Cambridge Laboratories, UK) to be given 5 days before the first irradiation at a dose of 125 mg twice daily by mouth. The drug was continued on radiation days until the end of the radiotherapy. The median overall dose of razoxane was 14 g per patient (range, 7.25-75 g). VDS was given intravenously at weekly doses of 2 mg. The median dose of VDS per patient was 43 mg (16-302 mg).

Three of the 21 patients in the razoxane/VDS group had been pre-treated with conventional chemotherapy, *i.e.* doxorubicin-based regimens, and 5 patients received that treatment during the later course of the disease. Furthermore, four patients had received 2-4 doses of mitoxanthrone in addition to the razoxane/VDS treatment. This initial treatment variant, however, was discontinued early because of chronic nausea.

Radiation therapy. External beam radiation therapy was performed with 6 MeV and 25 MeV photons with linear accelerators and conformal planning techniques. Single tumour doses between 170 and 200 cGy were given five times a week at the ICRU (International Comission on Radiation Units) point. The median total dose at unresectable primaries or recurrences was 60 Gy (range, 50-64 Gy) and 50 Gy (range, 50-60 Gy) at solitary metastases. In case of oligotopic metastases, the average total tumour doses were below 50 Gy. Six patients received two or more radiation series for metastases.

Control patients. Forty-one patients of similar age and similar prognostic features, in particular with similar stages of STS, who received contemporary cytotoxic drugs (doxorubicin-based regimens) in addition to radiotherapy served as controls. The control group was selected from 121 patients with adult-type sarcomas who were referred to our department between 1993 and 2002 for adjuvant or palliative radiation therapy, and from a further set of patients who between 1978 and 1988 had served as controls in a randomised study investigating the effects of razoxane when given in addition to radiotherapy (4).

To be elegible as controls, patients had to have unresectable primaries and/or early metastatic disease with fewer than 7 distant metastases at the time of referral. This cut-off level was an arbitrary decision. Patients with multiple metastases or patients with complete tumor resections who only received adjuvant radiotherapy were excluded as controls. For all patients serving as controls, complete clinical follow-up data as well as X-rays, CT and MRT imaging had to be available.

Response evaluation and follow-up. The radio-responsiveness was related to the clinical shrinkage of a tumour mass. The diagnosis of a complete response or remission (CR) required the complete disappearance of a tumour both clinically and on radiographic imaging. Partial regression (PR) was diagnosed with a reduction of the initial tumour volume by more than 50%, and disease progression was assumed if the pre-treatment tumour volume increased by 25% during or shortly after the end of the radiotherapy. Local tumour control was defined as no regrowth of the tumour at the site of irradiation as long as the patient survived.

All patients were followed up until December 2005 or to their death. Abdomino-pelvic and chest CTs were performed every 3 months during the first year. Additional investigations were carried out dependent on clinical needs. The number of new metastatic foci was counted every three months and the cumulative incidence of new metastases after 6 and 9 months was determined. In addition, progression-free survival at 6 months and the objective response rate of irradiated tumours was recorded. The survival time was calculated from the occurrence of the first distant metastasis and, additionally, from the beginning of the combination therapy (razoxane/VDS/radiotherapy) in the study cases or from any systemic cytotoxic chemotherapy and/or palliative radiotherapy in the control patients.

Statistical methods. The Wilcoxon-Gehan statistic was used to compare differences in survival times between the treatment groups. Other between-group differences were tested for statistical significance with the Mann-Whitney *U*-test for continuous variables and with the Chi-squared test for categorical variables, respectively. *P*-values <0.05 were considered significant. All statistical analyses were performed with the software package SPSS 11.0 for Windows (Chicago, IL, USA).

Results

The main pre-treatment characteristics of our patients including their relevant prognostic parameters are listed in Table I. There were no significant differences between the patients treated with razoxane/VDS and the controls.

Development of metastases. In the razoxane/VDS group, the median number of new distant metastases after 6 months was 0 (range, 0-40), and after 9 months likewise 0 (range, 0-70). The corresponding median values for the controls were 4.5 (range, 0-40) and 9 (range, 0->100) new metastases after 6 and 9 months, respectively (Figure 1). These differences in the occurrence of new metastases after 6 and 9 months were highly significant ($p=0.001$ and $p<0.001$, respectively).

In the subset of patients with unresectable primaries or isolated recurrences, none of the 7 patients treated with razoxane and vindesine developed distant metastases within 9 months, while 9 out of 13 control patients did ($p=0.045$).

Table I. *Clinical characteristics and prognostic factors of soft tissue sarcoma patients of this study.*

	Razoxane + VDS (n=21)	Controls (n=41)
Age in years (range)	61 (31-78)	59 (23-85)
Gender		
Male	11	22
Female	10	19
Time from diagnosis to metastasis in months (range)	11.5 (0-48)	9 (0-252)
Median largest tumor diameter at diagnosis in cm (range)	12 (5.5-23)	10 (2-25)
Histological diagnoses		
Liposarcoma	3	8
Malignant fibrous histiocytoma	1	8
Leiomyosarcoma	2	7
Fibrosarcoma	1	5
Angiosarcoma	7	3
Synovial sarcoma	1	3
GIST	1	3
Other rare entities	5	4
Histological grading		
1	2	2
2	4	7
3 + 4	13	26
Unknown	2	6
Conventional chemotherapy, ever given	8/21 (38%)	30/39 (77%)

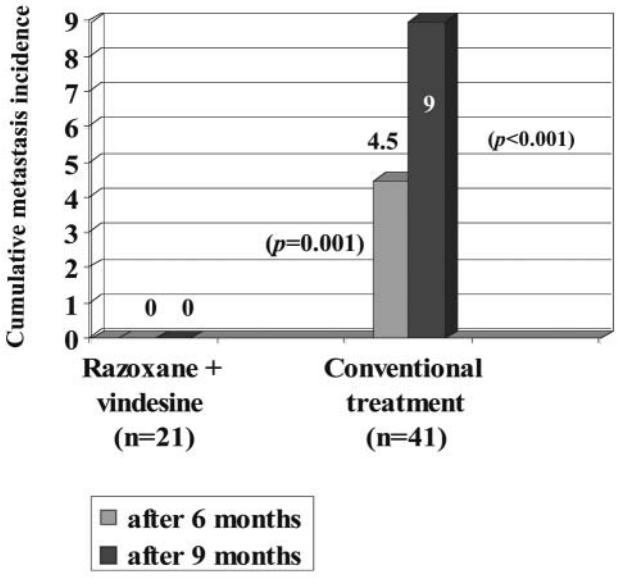

Figure 1. *Cumulative incidence of new metastases in soft tissue sarcomas after 6 and 9 months from start of the palliative treatment (median values).*

Survival. The median survival time from the occurrence of the first distant metastasis was 16 months (range 8-96+ months) in the anti-metastatic treatment group and 9 months (range 2-240 months) in the control group ($p=0.010$, Mann-Whitney *U*-test). Survival times from the beginning of a systemic drug treatment/palliative radiotherapy were 14 months (range 6-96+ months) in the study patients and 9 months (range 2-235 months) in the controls ($p=0.065$). The progression-free survival at 6 months was 71% in the patients treated with razoxane and vindesine and 23% in the controls, respectively ($p<0.001$).

Among the patients with unresectable primaries or recurrences without metastasis who received the anti-metastatic treatment the median survival has not yet been determined. Six of these 7 patients survived longer than 1 year compared to 5 out of 13 in the control group ($p=0.043$).

Radiation response. Among 17 assessable patients treated with razoxane/VDS, major clinical responses to radiation were seen in 15 patients (7 CR, 8 PR). Minor remissions were observed in 2 patients.

Twenty-one patients were evaluable in the control group. Major responses were observed in 13 patients (4 CR, 9 PR); this was significantly lower ($p=0.007$) than in the razoxane/VDS group. The control tumours did not change in size in 6 patients, tumour progression was noted in 2 patients.

Side-effects and complications (study group). The main side-effect of the combined razoxane/VDS/radiotherapy was leukopenia. Leukopenia of grade 3 or 4 was noted in 36% of the patients. The nadir of leukopenia was on day 16; no case of neutropenic fever occurred. Pulmonary embolism was seen in 3 patients, one with a lethal outcome. Other systemic toxicities included mild to moderate neurotoxicity, diarrhea grade 1-2 and nausea grade 1-2. In addition, we observed one case each of rib necrosis, Fournier necrosis of the gluteal region, severe headache and alopecia, respectively.

Normal tissue reactions were clearly enhanced by razoxane/VDS. Regional pneumonitis and esophagitis were most frequently observed when parts of the lung were irradiated. Such reactions occurred even with radiation doses of 30 Gy, but they were of limited clinical significance.

Discussion

From our data we conclude that the trimodal treatment with razoxane, vindesine and radiotherapy is feasible in patients with unresectable primaries and early metastatic STS. The combination inhibits the development of remote

metastases in the majority of patients, prolongs survival to some extent, and leads to a high rate of objective responses at irradiated tumour sites.

With the exception of gastrointestinal stromal tumours (GIST) for which survival advantages have been achieved with imatinib, the median survival in advanced soft tissue sarcomas has not substantially changed for almost three decades, irrespective of whether doxorubicin alone, doxorubicin with ifosfamide or cytoxan, vincristine, doxorubicin and dacarbacine (CYVADIC regimen) has been given (6, 20-22). The median survival time of advanced STS treated with contemporary chemotherapy ranges from 7-12 months (6, 22); a meta-analysis including 2185 patients showed an overall survival time of 51 weeks (21). In view of the unchanged prognosis of disseminated STS, a comparison of the results of this pilot trial with historical or non-randomized controls seems to be justified, especially if the prognostic features were not different among the compared groups.

Initial tumour size, histological grade, tumour site and lymph node involvement are the major prognostic factors for patients with primary STS (6). A long disease-free interval from diagnosis to first metastasis, low histopathological grade, young age, and absence of liver metastasis are the strongest predictors for a better prognosis in patients with disseminated disease (23, 24), while a doxorubicin-based chemotherapy did not affect the survival substantially (25). All these main prognostic factors did not differ significantly between the razoxane/VDS group and the controls.

The combination of razoxane and vindesine basically represents a combination of an angiogenesis affecting and a tubulin-inhibiting agent although the modes of action of the drugs are overlapping. Both drugs affect main steps of the metastatic cascade. Razoxane is strongly antimetastatic in animal systems (15, 17) but this had not yet been proven in man. Vindesine (VDS) was shown to be anti-invasive and thereby anti-metastatic by inhibition of the tubulin assembly (10, 11). VDS may also be applied to patients for several years without cumulative toxicity (8). By using similar combinations, *e.g.* long-term treatments with DC 101, a VEGF receptor-2-blocking antibody, together with the vinca-alkaloid vinblastin or the tubulin affinic drug paclitaxel, cures have been achieved in preclinical human neuroblastoma xenograft tumour models (26, 27).

Even though we had investigated only a limited number of patients, the results show a statistically highly significant anti-metastatic efficacy of the combination of razoxane and vindesine. The translation into a larger survival gain, however, seems to be of a modest degree as yet. Some reasons may account for this: A consistent long-term treatment with razoxane and vindesine was given to only 10 of the 21 patients of the trial. This was due to the fact that some patients were in a transient complete remission. In this situation there was no absolute need to continue the treatment, especially in a pilot study. Some patients also refused long-term treatment, others asked for a second opinion and were advised against this experimental treatment. Treatment-related side-effects were never a reason not to continue the treatment. In addition, the patients of this pilot study in general had a large tumour burden.

The determination of the rate of new metastases for a given period may represent an interesting clinical trial endpoint for the assessment of anti-angiogenic substances or, in general, of antimetastatic drug regimens. Presently, no basic data on the incidence and dynamics of metastases in STS are available from the literature. The retrospective evaluation of the metastatic process in the control group proved to be a cumbersome procedure. Numerous inquiries were necessary at different departments. In analyzing CT images and X-rays we had to face some imprecision, or even impossibility in counting metastases exactly, especially the lesions of the peritoneum or the pleura. Most precise data on the dynamics of the metastatic process in STS can probably only be obtained by a prospective trial with repeated whole body CT's. CT scans are associated with much higher numbers of visible lesions compared to chest X-rays. Hence, there remains some imprecision and the figures given on the numbers of metastases in this study must be seen and defined as minimal numbers of detected metastases.

The objective response rates at irradiated tumour sites under razoxane/VDS therapy were high in this study. Complete responses (CR) were observed in as many as 7 out of 17 assessable patients. For comparison, previously reported CR rates in STS treated by irradiation and intravenous radiosensitizers were 20% (3), and in STS treated with radiotherapy and razoxane 30% (4). Limited tumour shrinkage was observed by DeLaney *et al.* when neoadjuvant radiation therapy was combined with modern cytotoxic chemotherapy (28). Preoperative chemotherapy alone for extremity STS is associated with partial response rates between 27 and 40% (29, 30).

The trimodal combination therapy with razoxane, vindesine and radiotherapy is easy to perform. Patient compliance and tolerability of the drugs were satisfiying. No unsuspected toxicity was observed during long-term treatment, indicating the safety of the treatment. Caution should be given in irradiating larger lung volumes because of the danger of a pneumonitis.

Razoxane is a hitherto largely neglected antineoplastic agent although it has an interesting spectrum of modes of action and showed impressive clinical results. Unfortunately, in 2004, razoxane was discontinued by Cambridge Laboratories (UK) for economical reasons. An important question is now whether dexrazoxane

(Cardioxane®, Zinecard®) could be used instead of razoxane tablets. We think it should be tried. To date, limited clinical data are available on this issue but preclinical studies indicate that dexrazoxane may also synergize with radiotherapy (31). No unexpected toxicity was observed when dexrazoxane (and radiotherapy) was used together with doxorubicin and bevacizumab in STS to prevent cardiotoxicity (32).

In summary, the results of this pilot study suggest that a combined razoxane/vindesine treatment further increases the radioresponsiveness. The treatment seems to have the potential to reduce the propensity of STS for distant metastases. Anti-metastatic drug combinations supported by radiotherapy and/or surgery may become a new paradigm for the management of patients with unresectable primaries and oligometastatic STS. New rewarding areas of palliative or even curative radiation therapy of metastases may arise from this kind of treatment.

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