Cancer/Radiothérapie 20 (2016) 6–13

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Original article

Effective local control of advanced soft tissue sarcoma with neoadjuvant chemoradiotherapy and surgery: A single institutional experience

Contrôle local efficace des sarcomes localement évolués des tissus mous par chimioradiothérapie néoadjuvante et chirurgie : expérience d'un centre

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ARTICLE INFO

Article history:
Received 15 October 2014
Received in revised form 22 April 2015
Accepted 29 May 2015

Keywords:
Sarcoma
Neoadjuvant
Chemotherapy
Chemoradiotherapy
Radiotherapy
Toxicity
Survival
Recurrence

ABSTRACT

Purpose. – There is a sound theoretical basis but little clinical evidence substantiating the benefits of concurrent chemoradiotherapy with two-drug chemotherapy for locally advanced soft tissue sarcomas. Our five-year data on the feasibility and effectiveness of neoadjuvant chemoradiotherapy with systemically effective doses of adriamycin and ifosfamide combined is presented here.
Patients and methods. – Between 2000 and 2011, 53 patients with UICC (2010) stage I ($n = 1$, 1.9%), II ($n = 12$, 22.7%) or III ($n = 40$, 75.5%) nonmetastatic soft tissue sarcoma received neoadjuvant chemoradiotherapy with ifosfamide (1.5 g/m^2/day, d1–5, q28) and doxorubicin (50 mg/m^2/day, d3, q28) plus concurrent radiotherapy with a target dose of 50–64 Gy (median 60 Gy). The treatment of 34 patients (64.2%) was combined with hyperthermia.
Results. – At five years, the local control rate was 89.9% (± 5.7%), distant metastasis-free survival 66.6% (± 7.6%), and survival 83.3% (± 6%). The R0 resection rate was 81.1%. Radiotherapy was completed as planned in all patients and chemotherapy in 42/53 (70.2%). Grades III ($n = 21$, 29.6%) and IV ($n = 18$, 34%) leukopenia was the main acute adverse event. All acute and chronic non-hematologic toxicities were moderate.
Conclusion. – Neoadjuvant chemoradiotherapy for soft tissue sarcoma is associated with good feasibility, manageable acute and late toxicities, and high local efficacy.

Mots clés :
Sarcomes des tissus mous
Néoadjuvant
Chimioradiothérapie
Toxicité
Survie
Récidive

RÉSUMÉ

Objectif de l'étude. – Bien qu'il y ait une base théorique solide, peu d'études cliniques ont montré un avantage à l'administration d'une radiothérapie associée à une chimiothérapie dans le traitement des sarcomes de tissus mous avant la chirurgie. Nos résultats à cinq ans sur la faisabilité et l'efficacité de la chimioradiothérapie néoadjuvante avec des doses efficaces d'adriamycine et ifosfamide sont présentés ici.
Patients et méthodes. – Entre 2000 et 2011, 53 patients atteints d'une tumeur de tissus mous non métastatiques de stade I ($n = 1$, 1,9 %), II ($n = 12$, 22,6 %) ou III ($n = 40$, 75,5 %) selon la classification de 2010 de l'UICC ont reçu une chimioradiothérapie néoadjuvante avec ifosfamide (1,5 g/m^2/j, j1–5, q28) et doxorubicine (50 mg/m^2/j, j3, j28) associée à une radiothérapie concomitante de 50 à 64 Gy (médiane 60 Gy). Chez 34 patients (64,2 %), le traitement a été associé avec une hyperthermie.

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http://dx.doi.org/10.1016/j.canrad.2015.05.032

Résultats. – À cinq ans, le taux de contrôle local était de 89,9 % (± 5,7 %), celui du contrôle à distance de 66,6 % (± 7,6 %) et celui de suivi de 83,3 % (± 6 %). Le taux d'exérèse R0 était de 81,1 %. La radiothérapie a été réalisée chez tous les patients, la chimiothérapie chez 42 patients (70,2 %). Une leucopénie de grades III (n = 21, 29,6 %) et IV (n = 18, 34 %) représentait le principal effet secondaire aigu. La toxicité aiguë et celle chronique non hématologiques étaient modérées.
Conclusion. – Une chimioradiothérapie néoadjuvante pour les sarcomes des tissus mous est associée à une bonne faisabilité, une toxicité aiguë et chronique tout à fait acceptable et une bonne efficacité locale.

1. Introduction

Surgery and radiotherapy are standard treatments for soft tissue sarcoma and have made a significant contribution to improving the preservation of organs and functions in this prognostically heterogeneous group of patients. However, there is still room for improvement of local control in a number of critical situations [1–5], for example:

- when the primary tumour is unresectable or has inadequate margins for excision;
- when the tumour was inadequately resected and is not amenable to secondary resection (R2, R1, RX);
- or when adequate safety margins cannot be achieved due to tumour location, as is the case with soft tissue sarcomas in the head and neck region or retroperitoneal space.

Neoadjuvant chemoradiotherapy is useful in certain situations, for example, for the eradication of micrometastases in high-risk sarcoma patients and for preoperative cytoreduction.

Chemoradiation therapy has been an established treatment modality for many solid tumour entities for decades. Soft tissue sarcoma, however, is still considered an off-label indication for chemoradiotherapy because the extensive efficacy and toxicity data needed to establish it is still lacking. A few case studies and phases I and II trials have demonstrated the feasibility of chemoradiotherapy with different cytostatic agents alone (administered intra-arterially in some cases), or combined for the treatment of soft tissue sarcoma [6–8]. The scarcity of data on the use of systemically effective doses of adriamycin and ifosfamide combined is a particular problem. The effect of hyperthermia on chemoradiotherapy for soft tissue sarcoma is also being investigated [9]. The first data on the efficacy of neoadjuvant chemoradiotherapy for the treatment of soft tissue sarcomas was published in 1999 [10]. The present study aims to investigate the efficacy and toxicity of neoadjuvant chemoradiotherapy for locally advanced soft tissue sarcomas in a larger population of patients treated at our hospital in the last decade.

2. Material and methods

2.1. Patient selection

From 2000 to 2011, a total of 104 patients with soft tissue sarcoma, including 85 without distant metastases, were treated as described on Fig. 1. Only the 53 patients who received neoadjuvant chemoradiotherapy before surgery were included in the retrospective analysis. The remaining patients (n = 32) received adjuvant chemoradiotherapy. The radiology department's treatment register was used to identify the respective patients. Patient characteristics are summarized in Table 1.

2.2. Indications for neoadjuvant chemoradiotherapy

The indications for neoadjuvant chemoradiotherapy were as follows:

- unresectable or borderline resectable soft tissue sarcoma;
- unfavourable tumour location (retroperitoneum or head and neck region);
- high-risk tumour (tumour size ≥ 5 cm, grades II–III, deep/extracompartmental location) and;
- recurrent sarcoma.

Once the diagnosis had been confirmed by punch biopsy, the goal was to perform neoadjuvant chemoradiotherapy 6 to 8 weeks

Table 1
Patient and tumour characteristics (n = 53).
*Caractéristiques des patients et des tumeurs (*n = *53).*

	n (%)
Gender	
Male	34 (64.2)
Female	19 (35.8)
Age at first diagnosis	Median: 59 (21–76)
Primary tumour	47 (88.7)
Recurrent tumour	6 (11.3)
Histological type	
Liposarcoma	10 (18.9)
Pleomorphic sarcoma	13 (24.5)
Leiomyosarcoma	10 (18.9)
Synovialsarcoma	4 (7.5)
Myxofibrosarcoma	6 (11.3)
Other	10 (18.9)
Location	
Head/neck	1 (1.9)
Extremities	32 (60.4)
Upper extremity	6 (11.3)
Lower extremity	26 (49.1)
Trunk	6 (11.3)
Retroperitoneum	14 (26.4)
T stage	
T1	10 (18.9)
T2	43 (81.1)
N stage	
N0	51 (96.2)
N1	2 (3.8)
Grade	
G1	1 (1.9)
G2	23 (43.4)
G3	29 (54.7)
UICC I	1 (1.9)
IA: T1a–b N0 M0 low-grade	1 (1.9)
IB: T2a–b N0 M0 low-grade	0 (0)
UICC II	12 (22.6)
IIA: T1a–b N0 M0 high-grade	9 (17)
IIB: T2a N0 M0 high-grade	3 (5.6)
UICC III	40 (75.5)
T2b N0 M0 high-grade	39 (73.6)
Any T N1 M0 any grade	1 (1.9)
Tumour size	6–270 mm (median 80 mm)

UICC: Union for International Cancer Control.