EUROPEAN JOURNAL OF CANCER 47 (2011) 515–519

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Short Communication

Feasibility of metronomic oral cyclophosphamide plus prednisolone in elderly patients with inoperable or metastatic soft tissue sarcoma ☆

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ARTICLE INFO

Article history:
Received 9 September 2010
Received in revised form 22 November 2010
Accepted 26 November 2010
Available online 19 January 2011

Keywords:
Cyclophosphamide
Elderly
Sarcoma
Prednisolone
Radiation-induced sarcoma
Soft tissue sarcoma

ABSTRACT

Background: The number of elderly people with soft tissue sarcoma (STS) is increasing. A sizeable population of elderly patients with STS is unfit for conventional doxorubicin- or ifosfamide-based chemotherapy. We assessed the feasibility of metronomic oral cyclophosphamide (CPM) in this population.

Patients and methods: Patients aged 65 years or older with unresectable STS received CPM 100 mg twice daily plus prednisolone 20 mg daily, the first week of a 2-week cycle in the outpatient setting. Main evaluation criterion was safety. Secondary evaluation criteria were objective response rate and progression-free survival.

Results: Twenty-six patients (median age: 72, range 66–88) received a total of 330 cycles (median per patient: 10, range 2–41) as first ($n = 19$) or second-line chemotherapy ($n = 7$). The most frequent histological subtypes were poorly differenciated sarcoma ($n = 8$), leiomyosarcoma and liposarcoma (n = 5 each) and angiosarcoma ($n = 3$). Grade $\geqslant 3$ lymphopenia was observed in 81% of pts but no opportunist infection occurred. Grade 3 anaemia and thrombocytopenia occurred in 2 pts (8%) each. No other grade 3–4 toxicity was seen. The response rate was 26.9% (95%CI: 9.9–44.0) and the disease control rate (responses and stable disease >12 weeks) was 69.2% (95%CI: 51.5–87.0). One complete (hepatic epithelioid haemangio-endothelioma) and 6 partial responses (including 5 pts with radiation-induced sarcomas) were seen. Progression-free survival ranged from 0 to 20.6 months (median: 6.8 months) and was significantly longer in patients with radiation-induced sarcomas (median: 7.8 versus 5.2 months, $p = 0.02$).

Conclusion: Metronomic CPM showed good safety results for this frail population, with promising activity in patients with radiation-induced sarcoma. Toxicity profile was favourable, allowing prolonged home staying and rare treatment discontinuations. A larger prospective study is warranted to confirm these encouraging results in elderly with STS.

☆ This work was presented in part at the ASCO 2010 annual meeting (abstract 10065).

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0959-8049/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2010.11.025

1. Background

Soft tissue sarcomas (STS) are rare malignancies, with an estimated annual incidence of 10,000 new cases in the US.[1] Nearly one third of patients with STS are aged ⩾65 at diagnosis and 16% of those aged ⩾70 receive no treatment.[2] The number of elderly patients diagnosed and treated for STS is likely to increase in the forthcoming decades.[1] Although surgery is a viable treatment option in selected elderly patients with STS,[3] little is known on the medical treatment of elderly patients with inoperable and metastatic STS.

According to international guidelines, the treatment of patients with metastatic STS should be a first-line chemotherapy including anthracyclines.[4] Combination of doxorubicin plus ifosfamide or dacarbazine may be offered when a tumour response is expected to provide an advantage, taking into account the potential toxicity of multi-agent chemotherapy.

However, a sizeable population of elderly patients is not eligible for doxorubicin-based treatment, even for doxorubicin alone. Indeed, a number of elderly patients also have cardiac and respiratory co-morbidities making them at high risk for the use of cardiotoxic drugs such as doxorubicin.[5] Moreover, most patients aged over 70 years have an impaired renal function that precludes the use of ifosfamide. Impaired renal function can be due not only to age, but also to previous treatments and/or cancer.[6] Such patients unfit for standard chemotherapy and especially elderly patients are underrepresented in clinical trials, whereas they represent an increasing population in 'real life' medical oncology. As a consequence, there is presently no standard of care for the chemotherapeutic treatment of the elderly, unfit patients with inoperable or metastatic STS.

Oral cyclophosphamide (CPM) is active in a number of sarcomas, currently used in front line in some histological subtypes of sarcomas[7] and causes tolerable toxicity.[8] Metronomic schedules of CPM (i.e. long lasting administration of low doses, ranging from 50 to 100 mg/m^2/d) have been studied in breast and prostate cancers,[9,10] displaying clinical activity in some heavily pre-treated patients. Moreover, oral CPM can be safely administered in the outpatient setting.[11]

We report herein our single-centre experience with an outpatient regimen combining oral CPM and prednisolone in STS patients aged ⩾65 years. We show that despite a high-risk profile for acute toxicity, they could tolerate and benefit from

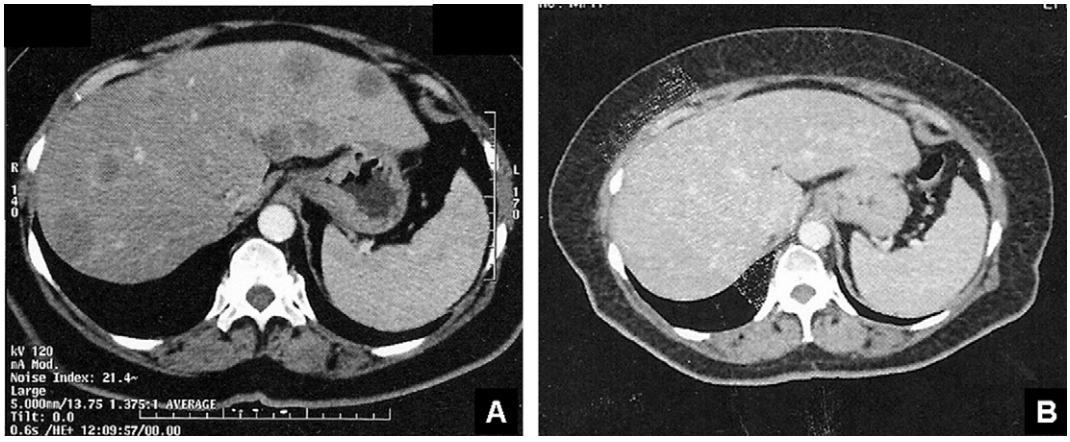

Fig. 1 – Abdominal CT-scans of a patient with hepatic hemangio-endothelioma before initiation of oral CPM (panel A), and after 2 months of treatment (panel B), showing a complete response.

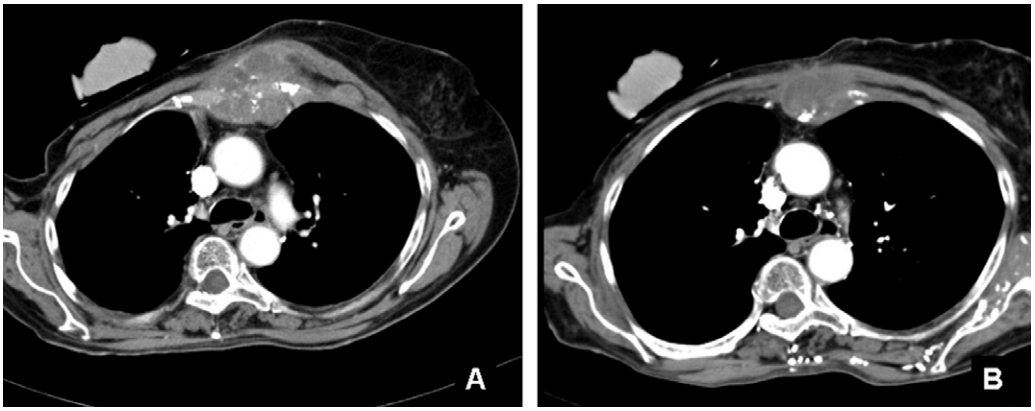

Fig. 2 – Thoracic CT-scans of a patient with radiation-induced sarcoma of the sternum before initiation of oral CPM (panel A), and after 6 months of treatment (panel B) showing a partial response.

this regimen, with dramatic responses in patients with radiation-induced sarcoma (RIS).

2. Patients and methods

We performed a retrospective electronical medical record review of elderly patients with inoperable or metastatic STS treated at the Institut Gustave Roussy between January 2001 and January 2009. During this period, more than 100 patients aged 65 years or older with adequate performance status and organ function received standard therapy based on doxorubicin, according to international guidelines. The remaining 26 patients were either found unfit for doxorubicin-based chemotherapy because of renal function impairment, severe cardiac or respiratory co-morbidities and/or poor PS ($n = 20$) or were pre-treated by doxorubicin ($n = 6$). These 26 patients were offered an oral metronomic chemotherapy schedule combining cyclophosphamide and prednisolone.

The treatment regimen included oral CPM 100 mg twice daily plus prednisolone 20 mg daily (administered on antiemetic purpose) given from day 1 to day 7 of a 14-d cycle. In 2 patients with a PS of 3, the dose of CPM was reduced to 50 mg bid. Complete blood cell count, serum chemistry and creatinine were monitored on day 1 by the treating physician. Patients received the instruction to maintain oral fluids intake of $\geqslant$1500 ml from day 1 to day 7.

All patients but 2 (in whom previous CT-scans were not available) had proven progressive disease according to the WHO criteria within 12 weeks before treatment initiation. Tumour evaluation was performed every four cycles of treatment, or before if clinically indicated, according to WHO criteria[12] Toxicity was assessed according to the NCI-CTC v3.0 criteria. Clinical benefit was defined as a 50% decrease in analgesic drugs requirements and/or improvement of PS. All patients were considered evaluable for toxicity and response rates were reported on an intent-to-treat basis. Progression-free survival and overall survival were measured from the date of first treatment administration to the date of disease progression or death for the former and the date of death for the latter.

Descriptive statistics were used to analyse patient characteristics [mean, median, 95% confidence intervals (CI)]. Kaplan–Meier estimates of the distribution of times from baseline to outcome were computed and the groups were compared using the log-rank test. Calculations were performed with NCSS™ 2007 software (NCSS, Kaysville, UT).

3. Results

Baseline characteristics of the 26 patients (median age 72 years, range 66–88) are summarised in Table 1. Hence, most patients had a PS of 2 or 3 and 19 patients (73.1%) had a Cockroft–Gault creatinine clearance $\leqslant$60 ml/min. The median number of metastatic sites was 1 (range: 1–3). The most frequent STS histological types were: poorly differenciated sarcoma ($n = 8$), leiomyosarcoma and liposarcoma ($n = 5$ each), and angiosarcoma ($n = 3$). Seventeen tumours (65.4%) were grade 3 sarcomas according to the FNCLCC scoring system.[13] The primary tumour site was axial in 18 patients (69.2%). Five tumours were RIS as defined by the Cahan criteria.[14]

Table 1 – Patients baseline characteristics ($n = 26$).

Characteristic	n (%)
Gender: M/F	6/20 (23.1/76.9)
Median age (range)	72 (66–88)
Median WHO PS (range)	2 (1–3)
Number of metastatic sites: median (range)	1 (0-3)
Primary site of STS	
Limbs	8 (30.8)
Retroperitoneum	8 (30.8)
Chest wall	4 (15.4)
Other	6 (23.1)
Histological subtypes	
Poorly differenciated sarcoma	8 (30.8)
Liposarcoma	5 (19.2)
Leiomyosarcoma	5 (19.2)
Angiosarcoma	3 (11.5)
Other	5 (19.2)
Tumour grade (FNCLCC scoring system): 2/3	9/17 (34.6/65.4)
Radiation-induced sarcomas	5 (19.2)
Co-morbidities	
Cardiac	5 (19.2)
Respiratory	4 (15.4)
Diabetes mellitus	2 (7.7)
Baseline CrCL (Cockroft-Gault) <60 ml/min	19 (73.1)
First/second line treatment	19/7 (73.1/26.9)

Abbreviations: PS, performance status; CrCl, creatinine clearance.

A total of 330 cycles were given (median per patient: 10, range 2–41). Nineteen patients (73.1%) received oral CPM as first-line therapy. Seven patients received oral CPM as second-line therapy. Six of them had received doxorubicin as first-line treatment, and one patient with angiosarcoma had received weekly paclitaxel.

Toxicity outcomes are presented in Table 2. The main grade 3/4 toxicities were: anaemia (grade 3:2 patients 7.7%), neutropenia (0 patients), thrombocytopenia (grade 3:2 patients, 7.7%), and lymphopenia (grade $\geqslant$3:21 patients, 80.7%). The CD4 count was obtained in 2 patients, and was <200/mm.[3] No febrile neutropenia occurred. No opportunistic infection was noticed. Nausea and emesis were mild and manageable. In all patients, underlying renal or cardiac function impairment remained stable and no acute aggravation of organ function requiring medical intervention was noticed.

Regarding treatment activity (Table 3), one complete (see Fig. 1) and six partial responses (see Fig. 2) were observed (including the 5 patients with RIS), for an overall objective response rate of 26.9% (95%CI: 9.9–44.0). Eleven other patients had a stable disease for $\geqslant$12 weeks, for an overall disease control rate (responses + stable diseases) of 69.2% (95%CI: 51.5–87.0). The median progression free survival was 6.8 (0–20.6) months and the 1-year survival rate was 65.4% (95%CI: 47.1–83.7). Amongst 8 patients with tumour-related pain, 4 had a clinical benefit as defined above. Five patients had an improvement of PS.

Remarkably, activity results in patients with RIS were better, with a progression-free survival of 7.8 months (range:

Table 2 – Toxicity profile (n = 26).

	All grades		Grade ⩾3	
	n	% (95%CI)	*n*	% (95%CI)
Lymphopenia	24	92.3 (82.1–100)	21	80.7 (65.6–95.9)
Anaemia	7	26.9 (9.9–44.0)	2	7.7 (0–17.9)
Neutropenia	5	19.2 (4.1–34.4)	0	0
Thrombocytopenia	6	23.1 (6.9–39.3)	2	7.7 (0–17.9)
Anorexia	6	23.1 (6.9–39.3)	0	0
Asthenia	8	30.8 (13.0–48.5)	0	0

Table 3 – Efficacy outcomes.

	All patients (*n* = 26)	Patients with RIS (*n* = 5)	Patients without RIS (*n* = 21)
Complete response: *n* (%)	1 (3.8)	0	1 (4.8)
Partial response: *n* (%)	6 (23.1)	5 (100)	1 (4.8)
Stable disease ⩾12 weeks: *n* (%)	11 (42.3)	0	11 (52.4)
ORR:% (95% CI)	26.9 (9.9–44.0)	100	9.5 (0–22.1)
PFS (months): median, range	6.8 (0–20.6)	7.8 (5.3–20.6)	5.2 (1.2–9.8)
1-year survival rate, % (95%CI)	65.4 (47.1–83.7)	80 (44.9–100)	61.9 (41.1–82.7)
OS (months): median, range	14.1 (1.2–30.4)	13.3 (11.3–30.4)	12.5 (1.2–26.1)

Abbreviations: RIS, radiation-induced sarcoma; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

5.3–20.6), significantly better than in patients with non-RIS (median: 5.2, range 1.2–9.8, $p = 0.02$).

Six patients received second-line therapy: 5 received oral etoposide on a compassionate basis and one (angiosarcoma) received weekly paclitaxel. In four other patients (including 3 RIS), CPM was stopped for patient's convenience after obtaining long-term (>6 months) stabilisation or partial response. At progression, the same regimen was reintroduced, resulting in 2 progressive diseases and 2 stabilisations (for 5.2 and 5.4 months, respectively, both patients having RIS).

4. Discussion

This single-institution experience with the combination of metronomic oral CPM and prednisolone in elderly STS patients suggests that chemotherapy may represent effective palliation in this setting, with a favourable toxicity profile allowing outpatient treatment with minimal impact on quality of life.

To our knowledge, this study is the first one dealing with safety and efficacy in elderly patients with STS treated by oral chemotherapy. Elderly patients are often excluded from clinical trials[15], and physicians lack adapted therapeutic options, especially in rare tumours such as STS. This study demonstrates that the treatment by CPM in metronomic schedule is feasible in elderly patients.

Indeed, safety was good, which is essential in frail elderly in palliative situation. There was no life-threatening adverse event. Biological toxicities were moderate and mainly haematological, with 81% of patients developing grade ⩾3 lymphopenia. Although lymphopenia was not associated with specific complications in this series, we hypothesise that patients receiving this regimen could be at high risk for opportunistic infections. Hence, patients receiving metronomic oral CPM could benefit from prophylactic anti-infectious treatments (trimethoprim-sulfamethoxazole and valaciclovir), as previously demonstrated in patients with deep lymphopenia.[16,17] Indeed, haematological toxicity can be a serious concern, even with metronomic chemotherapy schedules. Using a metronomic regimen of etoposide (100 mg/d orally, 3 weeks on 4), Italiano et al.[18] observed a disease control rate of 46% at 24 weeks in pre-treated STS patients. However, toxicity was pronounced with 1 grade 4 and 1 grade 5 febrile neutropenias. The authors underscored that the population that may derive benefit from this approach remains to be identified.

The objective response rate observed was in the range of what we observed with other more toxic chemotherapy agents classically used in this population. Even if this response rate was modest (26.9%, 95%CI: 9.9–44.0), it should be borne in mind that response may not be the best evaluation criterion in this population. Indeed, prolonged stable diseases may have an impact on quality of life, an important issue in elderly patients with inoperable disease. Moreover, oral treatment instead of IV chemotherapy may limit hospitalisations and enable patients to stay home longer. The prolonged duration of treatment by CPM (median number of cycles: 10, corresponding to 5 months) confirmed the safety and acceptability of the regimen.

The mechanism of action of metronomic oral CPM remains unclear, although it admitted that it combines anti-angiogenic effects and immunomodulation.[19,20] It is unknown whether these mechanisms could explain the unexpected activity observed in RIS, a specific subset of sarcomas poorly responsive to conventional chemotherapy.[21] However, the comparison between RIS and other sarcomas remains exploratory, and the small number of patients in this series does not allow drawing firm conclusions. Besides, prednisolone, although given on anti-emetic purpose in this

cohort, could also have played a role in the activity of this regimen.

Our study obviously presents some limitations: the population assessed is small and heterogeneous in terms of histological subtypes and proportion of RIS, and the retrospective method adopted limits statistical evaluation. However, the results are encouraging in a population presenting various poor prognosis factors, including age and co-morbidities.[22] Further prospective studies will confirm more accurately the efficacy of this regimen, in particular in patients with RIS, in whom we observed a progression-free survival ranging from 5.3 to 20.6 months.

5. Conclusion

Treating STS in unfit elderly patients is a complex issue, in the absence of any gold standard treatment. The metronomic oral CPM regimen is particularly interesting in this setting because of its safety and feasibility in the outpatient setting. Immunomodulation associated with anti-angiogenic action seems to be an original therapeutic approach in elderly STS patients. Specific immunity in elderly and molecular particularities of RIS have not been specifically studied yet. Further studies exploring the biological specificities of such malignancies may offer new therapeutic possibilities.

Conflict of interest statement

None declared.

Funding source

None.

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