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Gemcitabine Re-challenge in Metastatic Soft Tissue Sarcomas: A Therapeutic Option for Selected Patients

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Abstract. *Background/Aim: Treatment options for patients with metastatic soft tissue sarcomas are limited. Re-challenge with a previously successful gemcitabine-based regimen is common. There are no published data to support this practice. Patients and Methods: We conducted a retrospective search to identify patients re-challenged with gemcitabine-based chemotherapy (GBC) from 2003 to 2015. Results: Twenty-nine patients re-challenged with gemcitabine were identified. The response rate for initial GBC was 55% (n=15) and for re-challenge GBC 26% (n=6). The median progression-free survival was 11.1 months (95%CI=7.2-11.9) for initial GBC and 5.3 months (95%CI=2.0-7.5) for re-challenge GBC. Overall survival following gemcitabine re-challenge was 12.2 months (95%CI=7.0-18.2). Twelve out of 26 evaluable patients (46%) treated with re-challenge GBC experienced grade 3-4 adverse events (CTCAE 4.03) with 31% (n=8) of patients requiring dose reduction. Conclusion: In selected patients, gemcitabine re-challenge can be considered in advanced sarcomas, however, this approach is associated with toxicity.*

Soft tissue sarcomas (STS) are rare tumours that represent approximately 1% of adult cancers (1). STS comprise more than 60 different entities of which leiomyosarcoma (LMS), liposarcoma (LPS) and undifferentiated pleomorphic sarcoma are among the most common subtypes (2). For localized disease, surgery with or without neoadjuvant/adjuvant radiation is the mainstay of management (3, 4). The role of neoadjuvant/adjuvant chemotherapy is controversial, but it may be considered in patients with high risk of relapse (5, 6). Despite advances in therapy, approximately 50% of patients will develop recurrent/metastatic disease. The cornerstone of treatment for metastatic/locally advanced inoperable disease consists of palliative systemic chemotherapy.

Anthracycline-based therapy (either alone or in combination) is the standard first-line therapy (7, 8). Over the last few years, a number of new agents have been approved for 2nd and subsequent line therapy, including trabectedin, pazopanib and eribulin (9, 10). However, older chemotherapy drugs such as ifosfamide and gemcitabine still belong to the standard armamentarium for advanced disease.

Gemcitabine is a pyrimidine antimetabolite drug frequently used in combination with docetaxel. In a phase II trial conducted by the Sarcoma Alliance for Research through Collaboration (SARC) in unselected metastatic STS, the combination of gemcitabine plus docetaxel was superior to gemcitabine alone in terms of response rate (16% *vs.* 8%), median progression-free (6.2 *vs.* 3.0 months) and median overall survival (17.9 *vs.* 11.5 months) at the expense of a higher toxicity profile (11). The French phase II TAXOGEM trial, evaluated gemcitabine *vs.* gemcitabine docetaxel as 2nd-line therapy in patients with metastatic leiomyosarcoma. The endpoint of the study was response rate, which was 19% for gemcitabine alone and 24% for the combination arm (not statistically significant). The median progression-free survival was 6.3 months for non-uterine leiomyosarcomas treated with the combination compared to 3.8 months for the gemcitabine monotherapy arm (12).

Gemcitabine can also be combined with dacarbazine. In a phase II trial conducted by the Spanish Sarcoma Group (GEIS), gemcitabine plus dacarbazine was compared to dacarbazine alone in previously treated STS patients. The

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combination arm yielded a higher response rate (12% *vs*. 4%), as well as longer progression-free (4.2 *vs*. 2 months; HR=0.58; p=0.005) and overall survival (16.8 *vs*. 8.2 months; HR=0.55; p=0.014) (13).

Despite the recent advances and the incorporation of new drugs, treatment options for metastatic STS remain limited. Consequently, maximising the existing regimens by re-challenging selected patients who relapse after a reasonable interval with the same effective chemotherapy agent can be considered. Re-challenge with doxorubicin is not possible due to the risk of cardiotoxicity. In a retrospective study, ifosfamide re-challenge was found to be a viable option for metastatic STS, specifically synovial sarcoma (14).

Gemcitabine-based re-challenge may also be an option in selected patients previously benefitting from gemcitabine. To our knowledge, there are no published data supporting this strategy and therefore, the aim of this study was to evaluate the efficacy and toxicity of gemcitabine-based re-challenge in STS patients treated at a single referral centre.

Materials and Methods

Institutional approval was obtained prior to commencing the study (Royal Marsden Clinical Audit Committee approval 7/11/2017). The prospectively maintained Royal Marsden Sarcoma Unit database was retrospectively reviewed to identify patients re-challenged with gemcitabine between 2003 and 2015. Gemcitabine-based re-challenge was defined as treatment with gemcitabine as mono-therapy or in combination with another chemotherapy agent (docetaxel or dacarbazine) in any line and subsequent re-treatment with gemcitabine in a further line. Initial gemcitabine-based chemotherapy was defined as the chemotherapy line that gemcitabine was first used.

Clinical data and demographics as well as treatment details were obtained from the electronic patient records. This study was not limited to any specific histology and in all cases the histologic diagnosis was confirmed by a specialist STS pathologist (KT).

Chemotherapy schedules, response and toxicity assessment. Gemcitabine was administered as monotherapy at 1,200 mg/m^2 Days 1 and 8 every 3 weeks or in combination with docetaxel (gemcitabine 900 mg/m^2 or 675 mg/m^2 Days 1 and 8 and docetaxel 75 mg/m^2 Day 8) or dacarbazine (gemcitabine 1,800 mg/m2 Days 1 and 15 and dacarbazine 500 mg/m^2 Days 1 and 15). Re-challenge gemcitabine-based regimes could be the same as the first or differ at the discretion of the treating oncologist.

Response assessment was performed using CT scans. We retrospectively reviewed CT scans performed every 2 to 3 cycles using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Re-review of radiologic response was only possible for imaging performed from 2006 onwards (following installation of electronic archiving).

Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) were used to record grade 3 and 4 toxicities.

Statistical analysis. Clinical activity to gemcitabine-based chemotherapy (GBC) was measured following RECIST 1.1 as the percentage of patients achieving a complete response (CR) or a partial response (PR).

Table I. *Baseline characteristics*.

	Overall patients (N=29) N (%)
Age	
Median (range)	48 (30-60)
Gender	
Male	8 (28)
Female	21 (72)
Primary site location	
Uterus	16 (55)
Retroperitoneum	4 (14)
Extremities	4 (14)
Other	5 (17)
Histology	
Leiomyosarcoma	25 (86)
Angiosarcoma	1 (3.5)
Spindle cell sarcoma	1 (3.5)
Endometrial Stromal Sarcoma	1 (3.5)
Kaposi Sarcoma	1 (3.5)
Grade	
Low	2 (7)
Intermediate	7 (24)
High	14 (48)
Unknown	6 (21)
First GBC regimen	
Gemcitabine-docetaxel	25 (86)
Gemcitabine monotherapy	4 (14)
Re-challenge GBC regimen	
Gemcitabine-docetaxel	19 (66)
Gemcitabine monotherapy	9 (31)
Gemcitabine-DTIC	1 (3)

GBC: Gemcitabine-based chemotherapy; DTIC: dacarbacine.

Progression-free survival (PFS) for first GBC treatment was calculated from the first treatment date until disease progression and for second GBC from the first treatment date until disease progression, death by any cause or last follow-up.

Overall survival of the series was calculated from the original diagnosis date until death by any cause or last follow up. Overall survival (OS) after GBC re-challenge was calculated from the first treatment date of the second GBC treatment to the date of death by any cause or last follow-up. For OS and PFS analysis, survival curves and survival medians were estimated at 95% confidence using the Kaplan–Meier estimator. A 95% level of significance was used for all the statistical tests. All statistical analyses were done using the statistical software STATA version 13.1.

Results

Baseline characteristics. From 2003 to 2015 a total of 29 patients were re-challenged with gemcitabine-based chemotherapy (GBC). The median age at diagnosis was 48 years and 72% of the patients were female. The majority of patients were diagnosed with metastatic leiomyosarcoma (n=25, 86%) mostly uterine leiomyosarcoma (n=16, 55%) and the

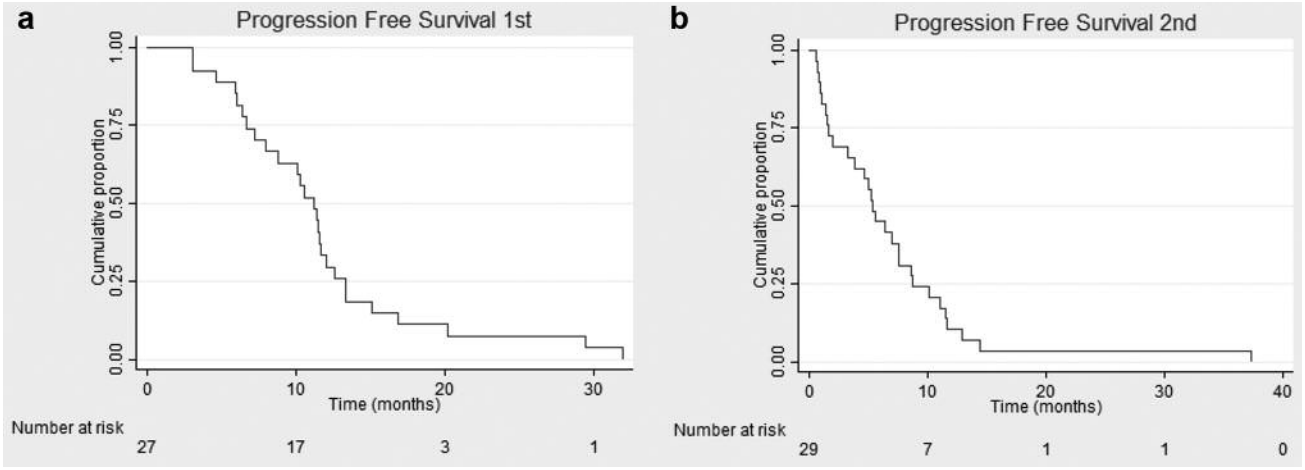

Figure 1. *Progression-free survival following initial and re-challenge gemcitabine-based chemotherapy. a) Progression-free survival following initial gemcitabine-based chemotherapy. b) Progression-free survival following re-challenge gemcitabine-based chemotherapy.*

majority of the tumours were intermediate to high grade (n=21). The baseline characteristics of this series are shown in Table I.

Response and toxicity

Initial gemcitabine-based chemotherapy. Thirty-eight percent (n=11) of patients received initial GBC as 1st-line therapy, 45% (n=13) as 2nd-line and 17% (n=5) as 3rd-line or greater. Twenty-five (86%) patients received gemcitabine plus docetaxel as initial GBC and the remainder gemcitabine alone as initial GBC. The median number of cycles administered was 5.4. Twenty-eight patients were evaluable for response, as one patient did not have RECIST measurable disease. The response rate was 55% (n=15).

Nine (31%) of the evaluable patients experienced grade 3-4 toxicity and 7 (24%) required a dose reduction.

Re-challenge gemcitabine-based chemotherapy. Re-challenge GBC consisted of gemcitabine-docetaxel in 66% (n=19), gemcitabine mono-therapy in 31% (n=9) and gemcitabine-dacarbazine in 3% (n=1) of patients. Re-challenge GBC was administered as 2nd-line therapy in 21% (n=6), as 3rd-line in 34% (n=10) and 4th-line/greater in 45% (n=13) of patients. The median number of cycles administered was 4.2. Twenty-three patients were evaluable for response and the response rate for gemcitabine re-challenge was 26% (n=6).

Twelve out of 26 patients (46%) treated with re-challenge GBC experienced grade 3-4 adverse events and 31% (n=8) required a dose reduction.

Only patients with leiomyosarcoma had RECIST radiological responses (n=15/25) to either initial or re-challenge GBC. No radiological responses were observed in the 4 other histological subtypes. A total of 5 patients had a response to initial GBC and also to gemcitabine re-challenge.

Progression-free and overall survival. The median PFS was 11.1 months (95%CI=7.2-11.9) for initial GBC. For re-challenge with gemcitabine-based chemotherapy median PFS was 5.3 months (95%CI=2.0-7.5) (Figure 1).

Following initial GBC, the majority of patients (n=23) had a PFS of more than 6 months. Two of the patients not achieving 6 months PFS had angiosarcoma and spindle cell sarcoma.

Following re-challenge GBC, a total of 16 patients had a PFS longer than 4 months.

The median overall survival from sarcoma diagnosis of this series was 50.6 months (95%CI=33.4-69.9). The median overall survival for patients treated with gemcitabine re-challenge was 12.2 months (95%CI=7.0-18.2) (Figure 1).

Discussion

Our retrospective study suggests that re-challenge with a previously successful gemcitabine-based regimen can be a therapeutic option for selected metastatic soft tissue sarcoma patients.

It is important to highlight that in our clinical practice we selected patients achieving a good and prolonged response with initial GBC before considering re-challenge with gemcitabine. Furthermore, we would not employ re-challenge GBC in those with progressive disease to initial GBC and those with a poor performance status.

In our study, the majority of patients had leiomyosarcoma (mostly grade 2 and 3) highlighting the higher sensitivity of this subtype to gemcitabine-based chemotherapy (15).

The majority of patients were treated with gemcitabine plus docetaxel as initial (55%) and re-challenge (25%) GBC.

The median PFS for initial GBC was 11.1 months, which is longer than that reported in prospective trials. This is

probably due to the inherent selection bias of this series (*i.e.* to be considered for re-challenge, patients had durable benefit to initial GBC). In the GeDDis trial, comparing 1st-line gemcitabine-docetaxel *versus* doxorubicin, the median PFS for gemcitabine-docetaxel was 6 months. The median PFS for re-challenge GBC was relatively long (5.3 months), considering many patients received re-challenge GBC as 4th-line or greater. Moreover, the median overall survival following re-challenge GBC was 12.2 months, but again this emphasises the selection of this chemo-sensitive cohort.

Gemcitabine plus docetaxel is associated with considerable toxicity. In the phase II trial published in 2002, the haematological grade 3-4 toxicities were 21% neutropenia (neutropenic fever 6%), 29% thrombocytopenia and 15% anaemia, and non-haematological grade 3-4 toxicities included 21% dyspnoea or 21% fatigue (16). In the phase III GeDDis trial, 285 serious adverse events were reported of which 111 (39%) were febrile neutropenia, fever and neutropenia, which led to 18% dose reductions (8). Other gemcitabine combinations or gemcitabine monotherapy have been associated with a lower percentage of severe adverse events (12, 13), but in our study fewer patients were treated with these regimens. Grade 3-4 toxicities in the re-challenge GBC setting were high (46%) and a considerable number of patients needed a dose reduction (31%). The fact that patients were treated in the 4th-line or greater may have contributed to this toxicity profile (*i.e.* heavily pre-treated). Therefore, when considering gemcitabine re-challenge the risk of increased toxicity should be discussed carefully with patients. If toxicity is a potential concern, then gemcitabine mono-therapy could be used.

The limitations of our study include its retrospective nature, the small number of patients, the lack of radiological review for some patients as well as the lack of patient reported outcome measures (which are particularly relevant in the setting of pre-treated advanced cancer).

Conclusion

The outcome of patients with metastatic soft tissue sarcoma remains poor with few systemic therapy options. Gemcitabine re-challenge could be a potential option for selected patients. Based on our results, patients with leiomyosarcoma achieving a PFS longer than 6 months following initial GBC could benefit the most. However, it is important to discuss the potential for toxicity carefully with patients, particularly if re-challenge is offered to heavily pre-treated patients.

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