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ORIGINAL PAPER

Chemotherapy in clear cell sarcoma

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Abstract Clear cell sarcoma is a rare translocation-related sarcoma. There have been few studies documenting the response rate and progression-free survival in clear cell sarcoma patients treated with palliative chemotherapy. The prospectively maintained databases of two referral centres were searched to identify clear cell sarcoma patients treated with chemotherapy. Twenty-four patients were treated with palliative first-line chemotherapy with a median age of 30 years at diagnosis. There were 18 men and 6 women. One (4%) achieved a partial response and 9 (38%) had stable disease. Fourteen patients (58%) progressed on therapy. The median progression-free survival was 11 weeks (95% CI, 3–20 weeks). The median overall survival from commencing first-line chemotherapy was 39 weeks (95% CI, 34–45 weeks). Second-line chemotherapy was administered to 12 patients, 11 (92%) of these progressed and one (8%) had stable disease. Of the 5 patients treated with third-line chemotherapy, 4 (80%) progressed and one (20%) had stable disease. One patient received fourth-line chemotherapy and maintained stable disease for 4 months. Conventional chemotherapy has minimal activity in clear cell sarcoma as documented by the response rate of 4% and median progression-free survival of 11 weeks in this retrospective series. These data provide a reference for response and outcome in the assessment of novel agents in this histological subtype.

Keywords Clear cell sarcoma · Chemotherapy · Response rate · Progression-free survival

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Introduction

Soft tissue sarcomas encompass a group of rare mesenchymal tumours that have widely differing behaviour and response to systemic therapy. Clear cell sarcoma (CCS) is a rare soft tissue sarcoma with melanocytic differentiation first described by Enzinger in 1965 [1] and was previously called melanoma of soft parts [2]. CCS has certain clinical features of melanoma (distal limb distribution, in-transit disease, regional lymph node spread and tendency for local recurrence) and soft tissue sarcoma (deep soft-tissue primary location and a propensity for pulmonary metastasis) [1, 3]. It has a predilection for the deep soft tissues of the lower extremity and typically involves the peripheral tendons and aponeuroses of young adults, although it has rarely been reported in the very young or elderly [3].

Microscopically these tumours display a uniform pattern composed of fusiform rounded cells with clear or eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli. The cells are divided into nests by thin fibrous septa, which are contiguous with adjacent aponeuroses or tendons. The clear cell appearance is due to the presence of large amounts of intracellular glycogen. On immunohistochemical evaluation these cells nearly always express S-100 protein, and most tumours also express antigens associated with melanin synthesis, such as HMB-45 and Melan-A. CCS is distinguished histopathologically from melanoma by the absence of a primary melanoma site or the absence of junctional activity within the overlying dermis.

Clear cell sarcoma is characterized by a translocation t(12;22)(q13;q12) and fusion of the *EWS* and *ATF1* genes [4, 5], that directly upregulate the microphthalmia transcription factor (MITF). This translocation has not been reported in melanoma. Tumours in the gastro-intestinal tract may have a variant fusion gene *EWSR1–CREB1* [6].

The mainstay of management is wide surgical resection with or without adjuvant radiotherapy. Despite adequate surgery, a large proportion of patients develop locally recurrent or metastatic disease. These tumours are aggressive and have a reported 5-year survival of between 40 and 67% [3].

Recently, the development of novel therapies in soft tissue sarcoma has been based on the histological subtype and a knowledge of the underlying biology. CCS is generally regarded as a chemo-resistant subtype, but there are limited data on the response and progression-free survival following palliative chemotherapy in this disease. Therefore, the aim of this study was to report the response and progression-free survival in a series of patients with CCS treated at two referral centres.

Materials and methods

Prior to commencing this study, approval was granted by the Institutional Review Board of both the Royal Marsden Hospital and Memorial Sloan-Kettering Cancer Center. A retrospective search of the Sarcoma databases at both institutions was performed to identify clear cell sarcoma patients treated with chemotherapy between 1990 and 2009. Patients referred for a second opinion only, rather than treatment, were excluded from the analysis. All pathology samples were reviewed by experienced soft tissue pathologists.

Date of diagnosis, age, gender, surgery, radiotherapy, chemotherapy regimen, response, date of progression and survival were obtained from the databases. Toxicity information was obtained from the hospital electronic patient record or hard copy notes. In the event of missing follow-up information, the patient's general practitioner or referring institution were contacted.

Chemotherapy regimens and response assessment

Patients were required to have a performance status (PS) of 0–2, prior to commencing chemotherapy. All patients underwent a pre-therapy CT scan. Response was assessed using WHO (World Health Organization) and RECIST (Response Evaluation Criteria in Solid Tumours) after 2–3 cycles of chemotherapy. Left ventricular ejection fraction was assessed using multigated acquisition (MUGA) scans in those receiving anthracycline-based therapy after every 2 cycles of treatment. Glomerular filtration rate (GFR) was evaluated following every 2 cycles of therapy in patients treated with ifosfamide. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria grading system and recorded at each clinic visit. Dose reductions due to toxicity were performed as per Unit guidelines. Following completion of chemotherapy, patients were followed up every 3 months, unless otherwise indicated. Some of these patients were treated within the context of Phase II and III trials. Following progression on conventional chemotherapy, patients were offered the possibility of participation in Phase I trials if their performance status, haematological, renal and liver function were adequate.

Statistical analysis

Median and range were used for continuous variables and proportions (%) for categorical variables. Progression-free and overall survival were measured from the start of chemotherapy until progression and death or last follow-up, respectively. Survival curves were calculated using the Kaplan–Meier method.

Results

Twenty-six CCS patients treated with chemotherapy were identified. Of these, 2 were treated with adjuvant chemotherapy but did not receive palliative systemic therapy. Twenty-four patients were treated with palliative first-line chemotherapy. Of the 24 patients, 18 (75%) were men and 6 (25%) women. The median age at diagnosis was 30 years. All patients underwent surgical resection of the primary tumour as initial management. At the time of analysis 22 patients had died and 2 were lost to follow-up.

The clinical characteristics of these patients are displayed in Table 1.

Neoadjuvant/adjuvant chemotherapy

One 28-year-old man received adjuvant radiotherapy and systemic therapy (interferon alfa-2B) following resection of a recurrent CCS in left axillary lymph nodes. He subsequently received systemic therapy (interferon alfa-2B and thalidomide) approximately 97 months later following resection of metastatic disease in the lung.

A 26-year-old man received adjuvant anthracycline-based chemotherapy after resection of a CCS in the right hip. He developed recurrent disease approximately 44 months later.

Two patients were treated with neoadjuvant chemotherapy and then went onto receive palliative chemotherapy on the development of recurrent disease. One of these patients was treated with MAID followed by ifosfamide, DTIC and liposomal doxorubicin and achieved a partial response to neoadjuvant chemotherapy. The response of

Table 1 Clinical characteristics of clear cell sarcoma patients treated with first-line chemotherapy

Characteristic	Number (%)
Age (median)	30
Gender	
Male	18 (75%)
Female	6 (25%)
Primary tumour site	
Lower limb	10 (42%)
Upper limb	9 (38%)
Trunk/viscera	5 (21%)
Primary tumour size (cm)	
≤5	6 (25%)
5–10	1 (4%)
10–15	2 (8%)
15–20	1 (4%)
>20	2 (8%)
Unknown	12 (50%)
Adjuvant radiotherapy	
Yes	12 (50%)
No	12 (50%)

the other patient to anthracycline-based neoadjuvant chemotherapy was not known.

Response to palliative chemotherapy

Twenty-four patients were treated with palliative chemotherapy. One patient (4%) achieved a partial response to first-line anthracycline-based chemotherapy. Stable disease was the best response recorded in 9 (38%) patients and 14 (58%) progressed on first-line chemotherapy. The regimen used and responses achieved are displayed in Table 2.

Twelve patients were treated with second-line systemic therapy, 11 (92%) of these progressed on treatment and one (8%) achieved stable disease.

Five patients were treated with third-line systemic therapy, 4 (80%) progressed on treatment and one (20%) maintained stable disease for 6 months.

One patient had stable disease following fourth-line chemotherapy, which was maintained for 4 months.

Progression-free and overall survival

The median progression-free survival following palliative first-line chemotherapy was 11 weeks (95% CI, 3–20 weeks). The Kaplan–Meier curve of progression-free survival is shown in Fig. 1.

The median overall survival from diagnosis was 32 months (95% CI, 24–39). The median overall survival from commencing chemotherapy was 39 weeks (95% CI, 34–45 weeks). The Kaplan–Meier curve of overall survival from first-line palliative chemotherapy is shown in Fig. 2.

Table 2 First-line chemotherapy regimens and responses achieved

Chemotherapy regimen	Response to first-line chemotherapy		
	Partial response	Stable disease	Progressive disease
Anthracycline	1 (4%)	6 (25%)	6 (25%)
Single agent	0	4	4
+ifosfamide	1	1	0
+platinum	0	1	2
Ifosfamide (single agent)	0	0	4 (17%)
Other	0	3 (13%)	4 (17%)
Cisplatin/vinblastine/DTIC			
+interferon	0	0	1
Cisplatin	0	1	0
Vincristine	0	0	1
Temozolamide + thalidomide	0	0	1
Sorafenib	0	1	0
Sirolimus	0	1	0
IGF1-R antibody	0	0	1

IGF1-R insulin-like growth factor 1-receptor

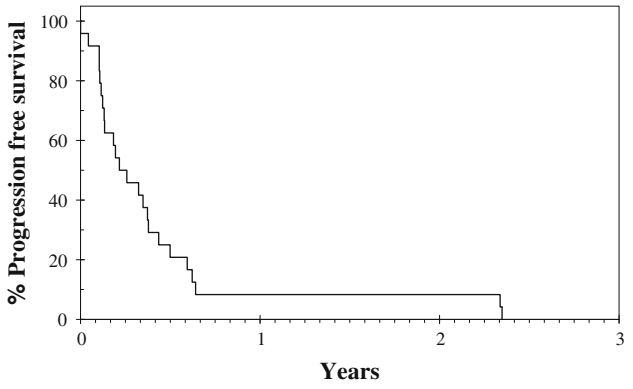

Fig. 1 Progression-free survival in clear cell sarcoma patients treated with palliative first-line chemotherapy

Discussion

Our study, showing a response rate of 4% and median progression-free survival of 11 weeks following first-line palliative treatment, indicates that conventional chemotherapy has little role to play in the management of CCS. In addition, one of the two patients treated with neoadjuvant systemic therapy achieved a partial response to an

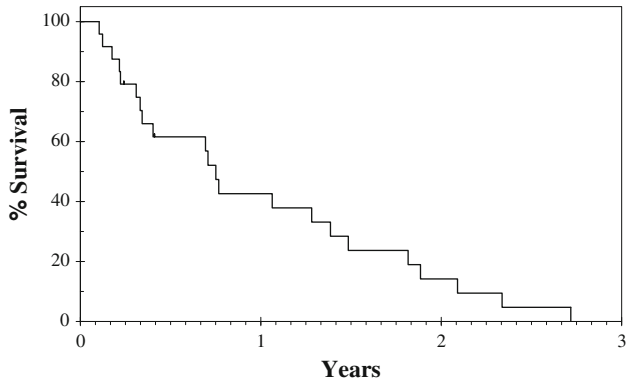

Fig. 2 Overall survival from commencing palliative first-line chemotherapy in clear cell sarcoma patients

anthracycline-based regimen. Although limited by small patient numbers and its retrospective nature, our study does provide a reference point for response and outcome, for the assessment of novel systemic therapies in CCS.

A number of retrospective studies have reported the application of varying chemotherapy regimens in this histological subtype [7–9].

The greatest activity of chemotherapy to date was noted in a report of the Japanese Musculoskeletal Oncology Group, who reported on a series of 30 adult CCS patients treated for metastatic and locally advanced disease [8]. Seven (23%) of these patients achieved a partial response to chemotherapy, all of whom were treated with regimens that included cisplatin. Additionally, they observed that 3 of the 4 patients treated with caffeine-assisted cisplatin showed objective tumour regression. In contrast, our results show a very low response rate to chemotherapy with a correspondingly short progression-free survival. The progression-free survival in the Japanese series was not reported. Furthermore, none of the 5 patients treated with first-line chemotherapy regimens containing a platinum complex in our study achieved a partial response. However, the utility of platinum-based therapy in this diagnosis merits further exploration, based on the results of the Japanese study.

The Italian and German Soft Tissue Sarcoma Cooperative Group reported on 28 young patients, aged between 2 and 21 (median 14 years), treated between 1980 and 2000 [10]. Chemotherapy was administered to 20 patients, of whom 7 were evaluable for response. One patient achieved a partial response and one a minor response. Five patients had no response. Other studies have reported varying activity of non-anthracycline-based regimens in adult patients with CCS [11, 12]. A retrospective study of the Dutch National Pathology Database identified 8 patients treated with doxorubicin-based regimens and one with a combination of bleomycin, vincristine, lomustine and dacarbazine [13]. One patient maintained stable disease for 7 months, but all other patients progressed. A number of other studies have reported the use of palliative chemotherapy in CCS, but have not recorded response or the response criteria used [7, 14–16].

The pathological similarities between CCS and malignant melanoma have led to the hypothesis that immunotherapy may have a role in the management of this condition. Steger et al. [17] reported a 17-month complete response to perilesional interferon alpha 2b (administered for 4 months) in a 40-year-old woman with CCS, but there have been few other reports of the use of immunotherapy in this disease [18].

Our data and the results of the other studies described above indicate that alternative strategies are required in the systemic therapy of this subtype. CCS is a MIT (microphthalmia transcription factor)-associated malignancy, together with alveolar soft part sarcoma and translocation-associated renal cell cancer. In CCS the characteristic translocation t(12;22)(q13;q12)/*EWSR1–ATF1* fusion activates MIT leading to overexpression of MET. MET is the receptor for hepatocyte growth factor (HGF), which is responsible for cell survival, adhesion, invasion, migration and angiogenesis. MET inhibition in these translocation-related neoplasms is currently being investigated in a Phase II trial (clinical trials.gov identifier NCT00557609) [19].

Pre-clinical studies have suggested that histone deacetylase (HDAC) inhibitors may have a role in the treatment of CCS [20, 21]. Liu et al. [20] observed that HDAC inhibitors induced apoptosis, inhibited cell growth and decreased mRNA levels of *EWS–ATF1* in CCS cell lines. Gene expression studies have identified other potential targets in CCS including fibroblast growth factor receptor 1 (FGFR1) [22]. Given the low response rates of CCS to standard cytotoxic agents, interferons and MET-directed therapy [19], these new potential mechanisms of action warrant further evaluation in prospective clinical trials, either as single agent therapy or in combination.

In conclusion, our retrospective study indicates that conventional chemotherapy has minimal efficacy in metastatic CCS as demonstrated by the low response rate and short progression-free survival. Ongoing pre-clinical and clinical studies of novel systemic agents will hopefully lead to improvements in progression-free and overall survival for patients with this rare condition.

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