Systemic treatment of advanced clear cell sarcoma: results from a retrospective international series from the World Sarcoma Network

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Background: Clear cell sarcoma (CCS) is a translocated aggressive malignancy with a high incidence of metastases and poor prognosis. There are few studies describing the activity of systemic therapy in CCS. We report a multi-institutional retrospective study of the outcomes of patients with advanced CCS treated with systemic therapy within the World Sarcoma Network (WSN).

Materials and methods: Patients with molecularly confirmed locally advanced or metastatic CCS treated with systemic therapy from June 1985 to May 2021 were included. Baseline demographic and treatment information, including response by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, was retrospectively collected by local investigators. Descriptive statistics were carried out.

Results: Fifty-five patients from 10 institutions were included. At diagnosis, the median age was 30 (15-73) years and 24% (n = 13/55) had metastatic disease. The median age at diagnosis was 30 (15-73) years. Most primary tumours were at aponeurosis (n = 9/55, 16%) or non-aponeurosis limb sites (n = 17/55, 31%). The most common fusion was EWSR1—ATF1 (n = 24/55, 44%). The median number of systemic therapies was 1 (range 1-7). The best response rate was seen for patients treated with sunitinib (30%, n = 3/10), with a median progression-free survival of 4 (95% confidence interval (CI) 1-7) months. The median overall survival for patients with advanced/metastatic disease was 15 months (95% CI 3-27 months).

Conclusions: Soft tissue sarcoma-type systemic therapies have limited benefit in advanced CCS and response rate was poor. International, multicentre prospective translational studies are required to identify new treatments for this ultra-rare subtype, and access to early clinical trial enrolment remains key for patients with CCS.

Key words: clear cell sarcoma, CCS, EWSR1—ATF1, soft tissue sarcoma, systemic therapy, chemotherapy, sunitinib

INTRODUCTION

Clear cell sarcoma (CCS) is an ultra-rare soft tissue sarcoma that often affects young adults with no sex preponderance.1-3 It often originates in limbs, specifically near aponeuroses and tendons.1 CCS is molecularly defined by reciprocal translocations involving EWSR1, with EWSR1—ATF1 [t(12;22)(q13;q12)] significantly more commonly seen than EWSR1—CREB1 [t(2;22)(q34;q12)].2,4

Driven by EWSR1—ATF1, microphthalmia-associated transcription factor (MITF) has been shown to be amplified in CCS.5 MITF plays a key role in regulating genes involved in cell growth, including BCL2 and MET.5,6 Despite this interesting biological rationale, treatment of 11 patients with CCS with the MET inhibitor tivantinib demonstrated an overall response rate (ORR) of only 9% (n = 1/11) and a disease control rate (DCR) of 36% (n = 4/11) and a median progression-free survival (mPFS) of 1.9 months.7 Another phase II trial with the MET inhibitor crizotinib (CREATE) showed an ORR of 3.8% (n = 1/28) and a DCR of 67.9% (n = 19/28), with an mPFS of 4.3 months.8 Tissue microarrays from patients enrolled in the CREATE trial8 demonstrated high levels of activation of pathways downstream of MET, including Grb2-associated binding protein 1 and mitogen-activated protein kinase, and copy number alterations in the region of MYC and COKN2A.8
Whilst the pathophysiology of CCS oncogenesis is actively investigated, there is a limited real-world understanding of the impact of systemic therapies on patients with advanced CCS as it is not well described in the literature. Small retrospective studies have reported that conventional chemotherapy used for soft tissue sarcoma has limited activity. We aimed to review the outcomes of patients with CCS treated with systemic therapies within the World Sarcoma Network (WSN) to further understand treatment for this ultra-rare sarcoma type.

MATERIALS AND METHODS

Institutional ethics approval (RMH SE1020) was mandated, and data transfer agreements were obtained between the Royal Marsden Hospital and participating institutions. Adults (age ≥15 years) treated with systemic therapy for advanced (unresectable or metastatic) CCS were identified from June 1985 to May 2021. Patients were identified from 10 participating sarcoma reference centres across 9 countries within the WSN. Written informed consent to treatment was obtained as per local standard of care.

Molecular confirmation of the diagnosis (EWSR1—ATF1, EWSR1—CREB1, or EWSR1 fusion with an unknown partner) was mandatory for patient inclusion. Demographics and treatment information were retrospectively collected by investigators at each site. Radiological treatment response was retrospectively assessed through imaging review, using the same cut-off values defined by Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1). Imaging was carried out as per institutional standards, which is generally every 2-3 cycles of therapy.

Descriptive statistics were applied, and mPFS and median overall survival (mOS) were calculated using the Kaplan—Meier method using SPSS statistics version 27 (IBM, Armonk, NY). Progression-free survival was defined as the time from the start of systemic therapy to radiological progression defined by RECIST 1.1. If radiological progression was unable to be obtained but there was overt clinical progression, then the date of clinical progression was used. Patients who remained on treatment and had not progressed at the time of data cut-off were deemed non-assessable. Overall survival was defined as the time from the diagnosis of metastatic disease to death from any cause. Patients who were alive at the data cut-off or were lost to follow-up were censored.

RESULTS

Fifty-five patients were identified from 10 institutions (Table 1) with a median follow-up of 22 months [95% confidence interval (CI) 16-24 months]. Molecular fusions included EWSR1—ATF1 (n = 24), EWSR1—CREB1 (n = 11), and EWSR1 fusion with an unknown partner (n = 24). The median age at diagnosis was 30 (range 15-73) years, there was an equal gender distribution, and most patients were of white ethnicity (47%). Over half of the patients had primary tumours of limbs. One-quarter (n = 13) of patients had metastatic disease at diagnosis. The median time to development of metastatic disease for those who presented with localized disease at diagnosis (n = 42) was 15 months (range 0-171 months).

Patients were treated with a variety of systemic therapies (Table 2). The most commonly used included conventional sarcoma chemotherapy regimens (~60% of patients with doxorubicin-based chemotherapy). The median number of systemic treatments used was 1 (range 1-7). The highest response rate was seen with sunitinib (n = 3/10, 30%), gemcitabine-based (n = 2/13, 15%), and doxorubicin-based (n = 4/34, 12%) chemotherapy. The mPFS for the entire cohort was 2 months (95% CI 1.2-2.7 months). The mOS for patients with advanced disease was 15 months (range 1-27 months) (Figure 1).

DISCUSSION

CCS is an ultra-rare sarcoma subtype. To our knowledge, this is the largest reported molecularly defined cohort of patients with advanced CCS treated with systemic therapy. The median age of our cohort was younger and patient gender more balanced than seen in the CREATE trial, but our cohort was otherwise similar to other published large retrospective cohorts. Most patients had aponeurosis or limb primary tumour site, in line with the available literature.

Since the frequent use of doxorubicin-based, gemcitabine-based chemotherapy and pazopanib within this series, CCS is generally treated with conventional systemic

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Table 1. Baseline characteristics of patients treated with systemic therapy

|                | n = 55 (%) |
|----------------|-----------|
| Median age (range), years | 30 (15-73) |
| Gender           |           |
| Male            | 28 (51)   |
| Female          | 27 (49)   |
| Ethnicity        |           |
| White           | 26 (47)   |
| Black           | 2 (4)     |
| Hispanic        | 7 (13)    |
| Asian           | 5 (9)     |
| Unknown         | 15 (27)   |
| Primary tumour site |         |
| Aponeurosis     | 13 (24)   |
| Non-aponeurosis limb | 18 (33) |
| Head and neck   | 1 (2)     |
| Intra-abdominal  | 7 (13)    |
| Thorax          | 4 (7)     |
| Pelvis          | 3 (6)     |
| Other           | 9 (13)    |
| Fusion status   |           |
| EWSR1—ATF1      | 24 (44)   |
| EWSR1—CREB1     | 11 (20)   |
| EWSR1—unknown partner | 20 (36) |
| Stage at diagnosis |       |
| Localized       | 42 (76)   |
| Metastatic/unresectable | 13 (24) |
| Time to development of metastatic disease (range), months | n = 42 |
|                | 15 (0-171) |
| Site of metastasis |         |
| Lung            | 26 (55)   |
| Bone            | 20 (36)   |
| Liver           | 6 (11)    |
therapies available for treatment of soft tissue sarcoma despite the poor evidence to support its use. All systemic therapies had a low response rate and a short mPFS. This is in line with other published cohorts.\(^9\) In a combined UK and US cohort of patients, there was a single response (\(n = 1/24\)) to doxorubicin in combination with ifosfamide and the mPFS was similarly short at 11 weeks.\(^9\) In our cohort, the highest response rate was seen with sunitinib. Small published cohorts\(^13\) and case reports\(^14,15\) have also supported the role of sunitinib in this population. The response rate seen for doxorubicin was similar to that for patients with unselected soft tissue sarcomas in the ANNOUNCE trial (ORR 14%, \(n = 36/258\)); however, the overall DCR was higher in ANNOUNCE (75.7%, \(n = 190/251\)) compared to 56% in our cohort. The mPFS for patients with CCS was shorter compared to the 6.8 months seen in ANNOUNCE.

Recent work by Schöffski et al. to profile CCS tumour samples from the CREATE trial has suggested alterations in five non-angiogenic-related pathways: PI3K-AKT, polymerase II transcription, DNA damage and mismatch repair, chromatin organization modifying enzymes and proteins involved in post-translational modification by small ubiquitin-like modifiers.\(^8\) Given the emerging evidence suggesting that epigenomic changes may play a key role in the oncogenesis of fusion-associated sarcomas, such as CCS,\(^16\) it is indeed intriguing that alterations in the CREATE

### Table 2. Response to systemic therapy

| Treatment                  | Number treated (\(n = 55\)) | Best response by RECIST 1.1, n (%) | Median PFS (95% CI), months |
|---------------------------|-----------------------------|-----------------------------------|-----------------------------|
| Doxorubicin based         | 34                          | 4 (12) | 15 (44) | 12 (22) | 3 (9) | 3 (0.9-4) |
| Pazopanib                 | 16                          | 0      | 0      | 3 (19)  | 9 (56) | 4 (25) | 1 (0-2)  |
| Gemcitabine based         | 13                          | 0      | 2 (15%)| 4 (31)  | 6 (46) | 1 (8)  | 3 (1-5)  |
| Sunitinib                 | 10                          | 0      | 3 (30) | 2 (20)  | 4 (40) | 1 (10) | 4 (1-7)  |
| Dacarbazine               | 9                           | 0      | 0      | 2 (22)  | 5 (56) | 2 (22) | 2 (NA)   |
| Trabectedin               | 7                           | 0      | 0      | 1 (14)  | 6 (86) | 0      | 1 (0.3-4)|
| Crizotinib                | 5                           | 0      | 0      | 1 (20)  | 4 (80) | 0      | 2 (0.9-3)|
| Checkpoint inhibitor      | 5                           | 0      | 0      | 2 (40)  | 3 (60) | 0      | 2 (0-6)  |
| Ifosfamide                | 5                           | 0      | 0      | 0      | 4 (80) | 1 (20) | 1 (NA)   |

CI, confidence interval; NA, not applicable; PFS, progression-free survival.

Figure 1. Median overall survival of metastatic/advanced patients.
cohort were seen related to epigenomic modifications. Drug treatments targeting such epigenomic changes, such as tazemetostat, are largely unexplored in CCS but may warrant further investigations. There are currently no actively recruiting clinical trials exploring the use of agents which target epigenomic alterations. There are currently no actively recruiting clinical trials exploring the use of agents which target epigenomic alterations. Beyond trials of immunotherapy, a phase I trial of anti-mitochondrial drug devimistat plus hydroxychloroquine (NCT04593758) was conducted. Given the aggressive clinical behaviour of CCS, it may be that a combination approach with epigenomic modifying drugs with chemotherapy may improve typically poor responses to cytotoxic sarcoma-type chemotherapy.

Given the short mPFS and low clinical benefit rate with sarcoma-type chemotherapy, an informed patient-clinician discussion is required to consider the use of standard cytotoxic chemotherapy. There has been interest in exploring the role of immunotherapy in the treatment of patients with CCS. In the phase IB portion of the IMMUNOSARC trial, there were two partial responses (n = 2/4) to nivolumab and sunitinib; however, the responses were of short duration. In the phase II OSCAR study, ORR was 7.1% in a combined cohort of patients with CCS and alveolar soft part sarcoma. Results of two additional ongoing phase II trials using dostarlimab (NCT04274023) and atezolizumab (NCT04458922) are expected in 2024. Results of these sarcoma-type-specific trials are awaited to further define the role of immune checkpoint inhibitors in this population.

Based on the results from our cohort, we advocate that CCS patients should be considered for early access to phase I trials. Given its ultra-rarity, rational design of prospective registries may be required to generate high-quality outcome-focused data to better understand the treatment and outcome of patients with CCS. If there is no clinical trial available, our data support the use of sunitinib first-line therapy in this population. We also advocate for tumour sequencing for patients with CCS in the hope of identifying novel treatment options. The decision to use cytotoxic chemotherapy requires a careful informed discussion between the patient and their oncology care team.

Our study has limitations that accompany all the retrospective cohorts. However, all patients had molecular confirmation of the diagnosis, which strengthens the results. All patients were treated at high-volume sarcoma centres within the WSN, with the expectation that similar standards of care were employed. The toxicity of treatment was not collected as this is difficult to extract retrospectively. The effect of radiotherapy and other local treatments was not explored in this cohort, and the impact of these treatments on the outcome of patients is not thoroughly known.

**Conclusion**

CCS is an ultra-rare sarcoma with a poor prognosis. In our series, response rate and mPFS with different systemic treatments were low. Sunitinib did demonstrate modest effectiveness compared to other therapies; however, sunitinib is not formally approved for the treatment of soft tissue sarcomas. Novel therapies for CCS are needed and the results of phase II studies with immune checkpoint inhibitors are awaited; however, it may be that epigenomic changes play a role in the oncogenesis of CCS. Prospective, translational registries are needed to further improve outcomes for this challenging population.

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