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CIC-DUX4 sarcomas

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Purpose of review
CIC-DUX4 sarcoma (CDS) is a high-grade undifferentiated round cells sarcoma that belongs to the undifferentiated round cell sarcomas family. It represents less than one percent of sarcomas, defining a rarest among rare malignancies. It affects young adults, displaying soft tissue mass. Considered very aggressive, a high proportion of cases display an advanced disease with lung metastasis at diagnosis. Here we discuss recent progress in molecular characterization of CDS, the main tracks of CDS biology and the current and future prospects of therapeutic approaches.

Recent findings
CDS is characterized by a specific oncogenic translocation *CIC::DUX4* that induce *ETV4* overexpression. Patients with CDS show an aggressive clinical course and have a significantly unfavorable outcome compared to Ewing sarcoma. As of today, there is a lack of consensus on whether they should be treated with an Ewing-like approach, as currently done by most sites, or regarded as high-grade soft tissue sarcoma (STS). Anyway, when feasible, combination regimens including anthracycline and alkylating agents should be favored and patients should not benefit from a therapeutic de-escalation. Overall, registration within clinical trials and prospective registries is recommended.

Summary
Overall, CDS showed a poor prognosis regardless of the patterns of treatment that warrant biological studies to better understand the disease.

Keywords
CIC::DUX4 sarcomas, *CIC*-rearranged sarcomas, ewing-like sarcoma, ultra-rare sarcoma, undifferentiated round cell sarcoma

INTRODUCTION

Sarcomas constitute a heterogeneous group of rare tumors of mesenchymal origin, representing <1% of all adult malignant tumors and 20% of childhood malignancies [1,2]. Pathology, immunohistochemistry (IHC) and molecular analysis currently allow the identification of more than 150 distinct subtypes. Within this family of rare tumors, Undifferentiated Round Cell Sarcomas (URCS) and Ewing Sarcoma (EwS) are a heterogeneous group of bone/soft tissue sarcomas characterized by small blue round cell morphology and overlapping IHC findings, nevertheless with diversified molecular abnormalities [3]. While Ewing Sarcoma is characterized by intense expression of CD99 and fusion of the *EWSR1* and *ETS* genes (most often EWSR1::FLI1), numerous and rarer URCS have subsequently been described recently.

According to the latest WHO classification of Soft Tissue Tumors and Bone [4▪▪], URCS are now kept separate from EwS and subclassified into three main subgroups: CIC-rearranged sarcomas (CRS), Sarcoma with BCOR genetic alterations and not ETS fused sarcomas. CRS are defined by a rearrangement of the Capicua transcriptional repressor (CIC) gene, mostly (95%) resulting from a gene fusion between *CIC* (19q13) and one of two double-homeobox (*DUX4*) retro-genes (4q35 or 10q26). Those CIC-DUX4 sarcomas (CDS) represent a highly aggressive subgroup of URCS that defines as rarest among rare malignancies (<1% of sarcomas). Previously classified as 'Ewing-like' sarcomas, CDS are mostly treated as such. However, although CDS and EwS share a

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KEY POINTS

- CDS is an ultra-rare subtype of sarcomas.
- Even if conventional cytotoxic chemotherapy regimens show efficacy in most patients, prognosis remain poor.
- Molecularly studies and new therapeutic options are urgently needed.

small blue round cell morphology, clinical, histological and molecular evidence suggest distinct entities. Importantly, CDS lacks the molecular hallmark of EwS. In this regard, the prognosis and management of CDS should be specifically addressed rather than extrapolated from EwS. In this review, we report recent advances in clinical, pathological, molecular characterization, pathogenesis and opportunities in innovative therapeutic approaches for CDS.

DESCRIPTION OF CIC-DUX4 SARCOMA

Epidemiology and clinical presentation

Even if the majority of URCS (60–70%) harbor a *CIC::DUX4* fusion, CDS remains an extremely rare disease, representing <1% of all sarcomas. There is a wide age range at presentation, from children to elderly adults, although most CDS occur in young adults in the age group of 15 to 35 years, with a slight male predominance. Main primary localizations are deep soft tissue in the limbs and trunk, and less commonly in the head and neck, retroperitoneum and pelvis. About 10% of cases occur in viscera including the kidney, gastrointestinal tract and brain, while primary osseous involvement is rare [5–7]. Superficial CDS are not infrequent and probably under-recognized [8–10]. Most cases follow a highly aggressive course and therefore are diagnosed at the time of metastatic stage. The most common metastatic site are the lungs.

Histopathology and molecular biology

CDS show the histopathological pattern of URCS, with diffuse sheets of undifferentiated, high-grade, slightly pleomorphic round cells, with a partial lobulated growth pattern, and inconstant fibrous stroma (Fig. 1). While IHC for CD99 stains CDS and does not help discriminate with EwS, strong expression of ETV4 is highly suggestive of CDS [11]. Molecular analysis confirms the diagnosis of CDS when demonstrating the *CIC::DUX4* fusion, resulting from a t(4;19)(q35;q13) or t(10;19)(q26;q13) translocation (Fig. 2). The chimeric gene involved *CIC*, which is a transcriptional repressor, and *DUX4*, a double homeobox transcription factor.

The CIC protein is an ortholog of the Drosophila melanogaster capicua gene and is a member of the high mobility group (HMG)-box superfamily of transcriptional repressors, which contains a conserved HMG domain that is involved in DNA binding and nuclear localization, and a conserved C-terminus. CIC has been shown to be essential for neuronal differentiation [12] and mutations in this gene have been associated with olidogdendrogliomas [13,14]. In the neuro-degenerative spinocerebellar ataxia type I disease, studies demonstrated that the N-terminal region of this protein interacts with ATXN1 to form a transcription repressor complex [15]. In cancer cells, recent studies have shown that the interaction between CIC and ATXN1L, a homolog of ATXN1, was involved in resistance to MAPK pathway inhibitors [16].

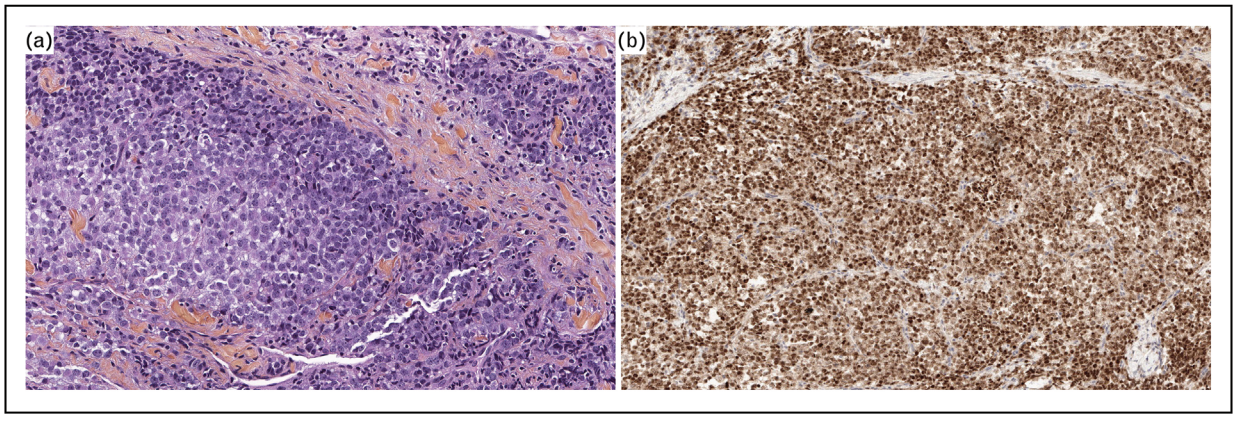


FIGURE 1. Histopathology of a CDS. CDS exhibits a lobular growth pattern with an URCS morphology. The proliferation is composed of sheets of round to epithelioid cells, with scant to moderate cytoplasm, and some degree of nuclear pleomorphism, with a high mitotic activity and frequent necrosis. By IHC, diffuse nuclear staining for ETV4 is present in >95% of cases.

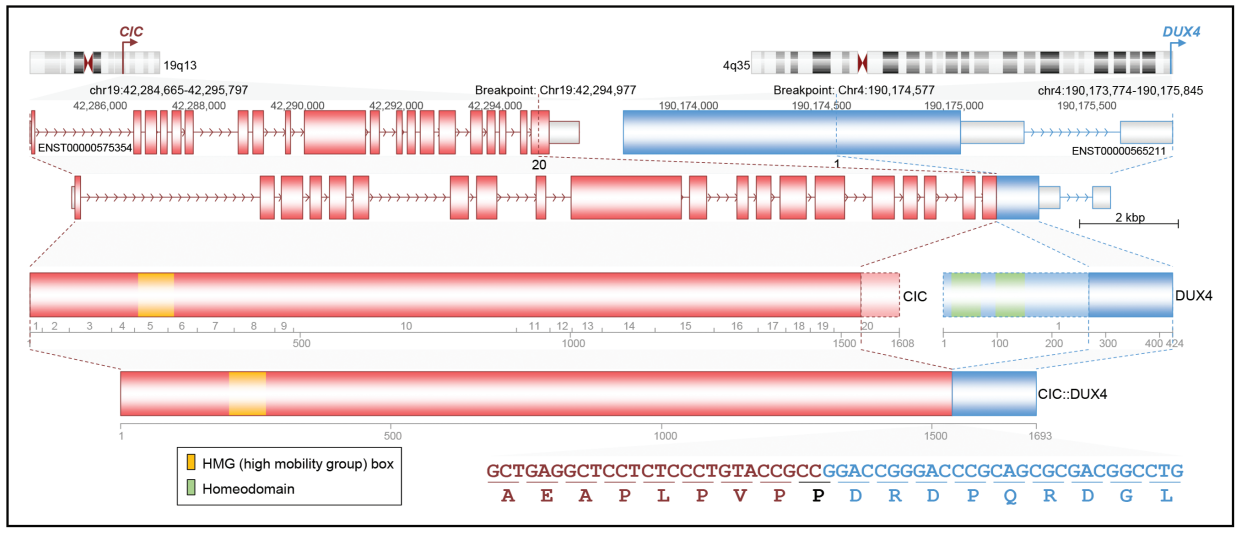


FIGURE 2. *CIC::DUX4* fusion. Schematic representation of *CIC::DUX4* fusion, which result from a t(4;19) translocation. The interrupted dark grey and light grey lines highlight the common breakpoints.

DUX4 is located within a D4Z4 macrosatellite repeat array in the subtelomeric region of chromosome 4q35 duplicated on the subtelomeric region of chromosome 10q26. The DUX4 protein is a transcriptional activator containing two DNA binding homeodomains in its N-terminus while the C-terminal domain is involved in transcriptional activation via interaction of EP300/CREBBP [17]. As an early embryonic transcription factor, it is normally silenced in somatic tissues but may be re-expressed in various solid cancers. Futhermore, inappropriate expression of DUX4 in muscle cells is the cause of facioscapulohumeral muscular dystrophy.

The CIC::DUX4 fusion protein enhances the transcriptional activity of CIC with subsequent upregulation of PEA3 family genes including *ETV1*, *ETV4* and *ETV5*, which explains why ETV4 IHC is highly suggestive of CDS [18–20].

Prognosis

Most of the studies reported so far include case reports or small series with limited follow-up data, which preclude definitive evaluation. Antonescu *et al.* [5] investigated the clinicopathological characteristics of a large cohort of CRS, to define their clinical presentation, morphological spectrum, and outcome. The study also examined the overall survival of the *CIC*-positive cohort compared to a control group of *bona fide* EwS with *EWSR1* gene fusion, matched for age and stage. The study cohort included 115 patients, with a mean age of 32 years and a slight male predominance. Most tumors occurred in soft tissues (86%), predominantly deep-seated and were equally divided between the trunk and extremity, followed by visceral locations (12%) and rarely bone (3%). The *CIC::DUX4* fusion was detected in 57% of cases, with *DUX4* in 4q35 (35%) or 10q26 in 25 (22%) cases. Clinical follow-up was available in 57 patients, with a 5-year survival of 43%, which was significantly lower than the 77% 5-year survival in the EwS control group ($P = 0.002$). Another cohort of 64 patients from the French Sarcoma Group recently reported at the 2021 ESMO congress recently confirmed a 4-year median overall survival (OS) for any stage diseases [21]. These results suggested an aggressive clinical course, with inferior OS compared to EwS.

THERAPEUTIC OPTIONS FOR CIC-DUX4 SARCOMA

Although no standard treatment has been established yet, previously published observations suggest that the management of this type of tumor should include a complete and large local excision, radiation therapy and neoadjuvant/adjuvant chemotherapy. Therefore, those so-called 'Ewing-like sarcomas' could be treated in the same way as classical EwS (neoadjuvant and adjuvant polychemotherapy, surgery and adjuvant radiation therapy) [22▪▪] or high-grade STS (neoadjuvant chemotherapy, surgery, adjuvant or neoadjuvant radiation therapy) [23]. However, there is no consensus on how to treat patients and studies are needed to define the optimal management of CDS. In addition, the management of recurrent/refractory CDS remains elusive.

Conventional chemotherapy

CDS have been reported to be less sensitive to a chemotherapy regimen used to treat EwS, in comparison to classical EwS. However, the literature

analysis reported several cases of good response to chemotherapy or radiation therapy Donthi *et al.* [24] reported in September 2020 the case of a 31 year-old patient who presented with an abdominal mass that was first treated by drainage. The final diagnosis was an URCS with *CIC-DUX4* translocation. The patient completed 14 cycles of chemotherapy based on EwS regimen, with etoposide and ifosfamide. He responded well to chemotherapy and did not report any metastatic spread at 2 years. Furthermore, A. Cristini Vieira *et al.* [25] reported the case of an uterine CDS exhibiting a nearly complete pathological response after radiation therapy and neoadjuvant chemotherapy. In fact, the patient received hypofractionated hemostatic radiation therapy at a total dose of 12 Grays (Gy) divided into 3 fractions of 4 Gy followed by neoadjuvant chemotherapy with vincristine, doxorubicin, cyclophosphamide in alternation with ifosfamide and etoposide (VDC/IE), according to standard protocols applied to EwS. Restaging revealed complete response by CT and MRI after four cycles of systemic therapy. The patient then underwent a bilateral salpingo-oophorectomy and total hysterectomy, without lymph-node dissection. The pathological report revealed a near-complete tumor regression.

Steven Christopher Smith *et al.* [26] reported a cohort of 10 cases of CDS patients. Among them, two cases showed metastatic progression with prolonged survival after combination chemotherapy (including the Ewing sarcoma regimen, VDC-IE) and radiotherapy, without evidence of disease at 22 and 48 months. These results suggest that a multidrug Ewing sarcoma-type regimen may be advantageous in these patients.

Recently, the FSG reported a retrospective study that describe characteristics, treatments and outcome for 64 patients with CDS [21]. Two groups of patients were studied: those treated in the same way as classical Ewing sarcomas and those treated in the same way as high-grade STS. The characteristics of the population and tumors were not statistically different between cohort 1 (66%) and cohort 2 (34%). The median overall survival from diagnosis was 4 years, with no significant differences between both cohorts ($P = 0.99$). However, when focusing on patients with metastatic disease at diagnosis ($N = 18$), all patients in cohort 2 had died of the disease while some patients in cohort 1 are still alive and in complete remission, resulting in significantly better OS ($P < 0.05$). FSG experience confirms the aggressive clinical course of CDS and even if the best therapeutic strategy is currently uncertain, this study suggests that patients should not benefit from a therapeutic de-escalation, especially in the case of metastatic disease.

Translational research

Currently, several patient-derived CDS cell lines have been reported. Yuki Yoshimatsu *et al.* [27] have established and characterized the NCC-CDS2-C1 cell line using surgically resected tumor tissue from a patient with CDS. NCC-CDS2-C1 cells harbored a *CIC::DUX4* fusion without insertion and exhibited rapid growth, spheroid formation, and invasion. Bosnakovski *et al.* [28▪] have demonstrated that the CIC::DUX4 chimeric protein requires P300/CBP to induce histone H3 acetylation, activate its targets, and drive oncogenesis. They have described the synthetic route to a selective and highly potent P300/CBP inhibitor named iP300w and related stereoisomers, and found that iP300w efficiently suppress CIC::DUX4 transcriptional activity and reverses CIC::DUX4 induced histone H3 acetylation. The effectiveness of iP300w in inactivating CIC::DUX4 highlights epigenetic modulators as a promising therapeutic opportunity for CDS. Nakai *et al.* [29] successfully established a new human CDS cell line designated Kitra-SRS and developed orthotopic tumor xenografts in nude mice. The *CIC::DUX4* fusion gene in Kitra-SRS cells was generated by complex t(12;19) chromosomal rearrangements with an insertion of a chromosome segment that included DUX4 pseudogene component. Kitra-SRS xenografts were histologically similar to the original tumor and exhibited metastatic potential to the lungs. Kitra-SRS cells showed autocrine activation of the insulin-like growth factor 1 (IGF-1)/IGF-1 receptor (IGF-1R) pathway. Consequently, treatment with the IGF-1R inhibitor, linsitinib, attenuated Kitra-SRS cell growth and IGF-1-induced activation of IGF-1R/AKT signalling both in vitro and in vivo. *CIC::DUX4* was also described by a negative regulation of the MAPK pathway due to an upregulation of downregulators such as dual specificity phosphatases DUPS6 [30]. Therefore, unlike some other cancers where MAPK is to be targeted, inhibiting DUSP6 led to increased ERK activity to degrade CIC::DUX4 *in vitro*.

ARO-DUX4 is a drug designed to target the DUX4 protein as a potential treatment for patients with CDS [31]. As reported in the publication of Okimoto *et al.*, [32] CDS sarcomas are characterized by a dependence on the CCNE-CDK2 cell cycle complex that makes CIC-DUX4-expressing tumors sensitive to inhibition of the CCNE-CDK2 complex. It is noteworthy that a selective CDK2-E inhibitor (BLU0298) is currently being investigated in preclinical experiments for its potential as anticancer agents in cancers affected by aberration of CCNE [33]. Guo-Liang Chew *et al.* [34] reported that DUX4-expressing cancers were paradoxically characterized by reduced markers of antitumor cytolytic activity and lower expression of the class I gene of the major histocompatibility complex (MHC).

DUX4 expression blocks interferon-g-mediated induction of MHC class I, implicating suppressed antigen presentation in DUX4-mediated immune evasion. Clinical data in metastatic melanoma confirmed that DUX4 expression was associated with significantly reduced progression-free and overall survival in response to anti-CTLA-4.

Clinical research

CDS were included in the Euro-Ewing 2012 clinical trial (NCT00987636). As of now, the future European trial of Ewing sarcoma will probably continue to include CDS patients even if they will be evaluated separately. The multinational multi-tumor prospective phase II clinical trial (NCT02389244) initiated by the FSG aims to evaluate the efficacy and safety of regorafenib in patients with advanced tumors including recurrent/refractory CDS.

DISCUSSION

URCS represent a heterogeneous group of tumors, affecting mostly children and young adults and characterized by a generally poor prognosis. Most cases remain challenging for pathologists and require specific IHC and molecular investigations, requiring expert consultation that can benefit from clinicopathological networks [35]. Specific fusion transcripts have defined their diagnosis, as a specific fusion gene that characterizes most subtypes. Therefore, the recent publication of the new WHO classification of Soft Tissue Tumours and Bone [4▪▪] subclassified URCS according to the underlying gene rearrangements, including the family of CRS. While *DUX4* is the most frequent partner (95%) [4▪▪], alternative CIC partners include *FOXO4*, *NUTM1*, and *NUTM2A* [36–38].

As a result, demonstration of specific chromosome translocations by FISH and fusion transcripts bi-targeted RT-PCR, anchored multiplex PCR (Archer) and whole-exome RNA sequencing have become an asset for the molecular diagnosis of URCS. CDS is now easily suggested with the help of ETV4 IHC and subsequently confirmed by molecular biology. In addition to the fundamental role of expert pathology, rapid molecular analysis plays a pivotal role in the diagnosis of URCS. In this regard, some biopsy material should be preserved for molecular techniques when confronted with a histological pattern of URCS.

CDS represent a highly aggressive tumor with a poor prognosis, as compared to EwS. Literature on CDS remains scarce, with mainly retrospective data and therefore the biases that are related and inherent to these types of studies. Anyway, CDS were enrolled in the latest Euro-Ewing 2012 clinical trial prospective data will be available soon. Currently, patients are routinely treated in the same way as EwS and STS, with an anthracycline-based polychemotherapy regimen. Classical chemotherapy might be very efficient and de-escalation should not be considered as of now, until better-targeted treatment is discovered. Unfortunately, CDS patients with recurrent/refractory disease have limited therapeutic options. Importantly, the results of the REGOBONE trial (NCT02389244) are eagerly awaited. Furthermore, inclusion of CDS patients in clinical trials should be encouraged from the first line.

The management of such rare subtypes of sarcomas is challenging, especially in advanced stages. Indeed, clinical research dedicated to rare cancers is complicated by recruitment difficulties and face the lack of interest of drug developers in this very limited economic potential.

CONCLUSION

The management of ultra-rare sarcoma [39] is challenging, especially in advanced stages. Indeed, clinical research dedicated to rare cancers is complicated by recruitment difficulties and faces the lack of interest of drug developers in this very limited economic potential. Therefore, international collaborative studies with academic funding are probably the best way to consider this. Otherwise, improvements in molecular diagnosis cannot immediately be translated into better understanding of tumorigenesis mechanisms or development of targeted therapies.

Among the family of URCS, CDS are currently recognized as distinct entities, with distinctive molecular, IHC, clinical and epidemiological features, as detailed earlier. Anyway, the precise mechanisms of tumorigenesis remain elusive. Even if there is no consensus on the best therapeutic strategy, combination regimens including anthracycline and alkylating agents should be favored when feasible. Registration in prospective clinical trials and registries is highly recommended.

What should be the next steps? For recurrent/refractory disease, more prospective studies are warranted to evaluate the benefit of antiangiogenetic and/or new drugs in advanced CDS are warranted. At initial management, can antiangiogenics (in the adjuvant or neoadjuvant setting) improve the outcome of patients? The first results of the REGOBONE phase II study (NCT02389244) will provide a lot of useful information (and a phase 1 study in Ewing Sarcoma will evaluate the addition of Regorafenib to VDC/IE). In addition, more than ever, translational ancillary studies remain essential to understand mechanisms of action and prediction of response.

International collaboration and long follow up would be mandatory.

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Conflicts of interest

There are no conflicts of interest.

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