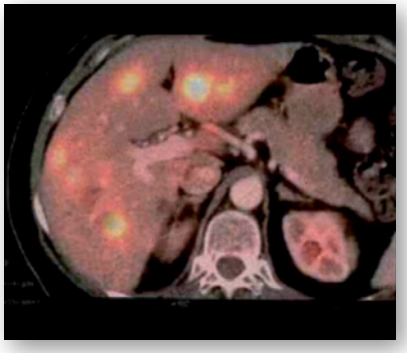

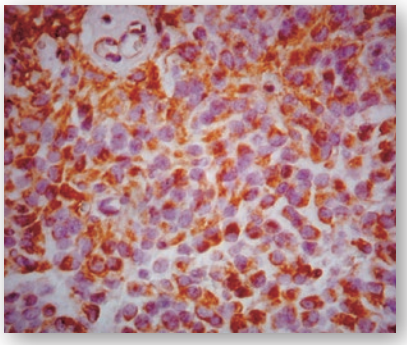

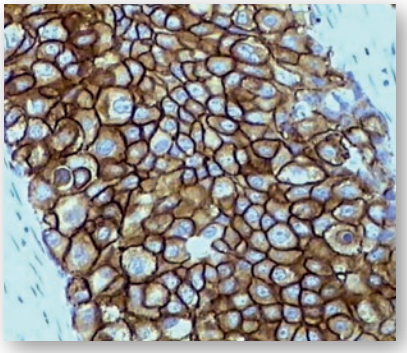

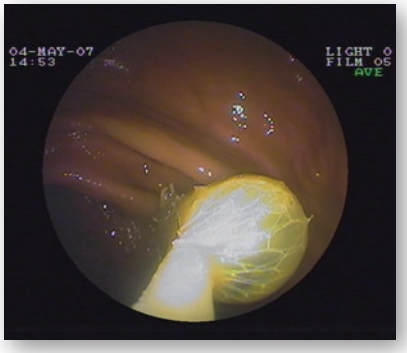

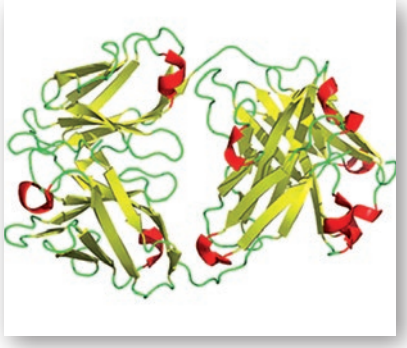

Cancer & Chemotherapy Reviews

Volume 17 - Number 3 • 2022 • ISSN: 1885-740X

http://**www.cancerchemotherapyreviews.com**

Indexed in EMBASE/Excerpta Medica

Permanyer
www.permanyer.com

A scientific initiative of the ECO Foundation

Cancer & Chemotherapy Reviews

Volume 17 - Number 3 • 2022 • Published quarterly • ISSN: 1885-740X
http://www.cancerchemotherapyreviews.com
Indexed in EMBASE/Excerpta Medica

A scientific initiative of the ECO Foundation

eco Fundación para la Excelencia y la Calidad de la Oncología

PERMANYER
www.permanyer.com

Annual Subscription Order Form to **Cancer & Chemotherapy Reviews**

ISSN: 1885-740X

Published quarterly

Print edition

☐ Personal subscription: € 130.00

☐ Corporate subscription: € 230.00

Electronic edition

☐ Personal subscription: € 100.00

☐ Corporate IP subscription: (quotation without compromise, please contact suscripciones.cancer@permanyer.com with information about quantity and type of IP's)

PAYMENT OPTIONS:

☐ I enclose a check made payable to P. Permanyer, S.L.

☐ I wish to pay by credit card: ☐ VISA ☐ MASTER CARD

Card number: ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Expiry date: ☐☐ / ☐☐☐☐

Signature:

Name (capitals):

Address:

Country: Postcode:

Phone:

E-mail:

Send Orders to:

P. PERMANYER, S.L.

Subscription Department

Mallorca, 310 - 08037 Barcelona - Spain

Phone: +34 93 476 01 76

E-mail: permanyer@permanyer.com

For the purposes set forth in Organic Law 15/1999, on Personal Data Protection, we inform you that the personal data furnished in this bulletin shall be included in a filed created under the direction of **PUBLICIDAD PERMANYER, S.L.**, in order to fulfil your request for subscription. You have the right to access the information regarding yourself collected in our file, to correct the data if it is incorrect or cancel it, as well as to oppose processing of such data at the following address: **PUBLICIDAD PERMANYER S.L., Mallorca 310, 08037 BARCELONA - Administration Department**.

Signed: The interested party

PERMANYER
www.permanyer.com

Mallorca, 310 - 08037 Barcelona (Catalonia), Spain
Phone: +34 93 207 59 20

ISSN: 1885-740X/2339-8728 • **Legal deposit:** B-47.879-2006 • **Ref.:** 7290AM221

Contact:
permanyer@permanyer.com

www.permanyer.com

TCF Printed on acid-free paper

This paper meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of paper)

Definition of ultra-rare sarcomas and their challenges

Jean-Yves Blay

Centre Léon Bérard, Lyon, France

Rare cancers are defined as malignancies with an incidence of < 6/100,000/year[1]. Many sarcoma subtypes are exceedingly rare and being labeled as ultra-rare. Recently, a consensus from the Connective Tissue Oncology Society (CTOS) reached a definition and a list of ultra-rare sarcomas with the intention of increasing awareness and direct research efforts to find new therapies[1]. Ultra-rare sarcomas were defined as those with an incidence of approximately ≤ 1/million, to include those entities whose rarity renders them extremely difficult to conduct well powered, prospective, and clinical studies[1]. Accordingly, 56 different subtypes have been included in the list of ultra-rare sarcomas, which represents 20% of all soft tissue and bone sarcomas (STS)[1] (Table 1).

Incidence data over 4 years (2013-2016) for sarcomas and connective tissue tumors of intermediate malignancy (TIM) in France have recently been published[2]. The database of the national reference networks for sarcomas and TIM was used and reviewed by a large network of specialists. More than 150 different histological subtypes were detected in 25,172 patients with sarcoma (74.3%) or TIM (25.7%). During these 4 years, the annual incidence of sarcomas and TIM was 70.7 and 24.4, respectively, with a combined incidence of 95.1/10^6/year, higher than the previously reported incidence. The study showed a variation in the individual incidence of different sarcoma histotypes between 10/10^6 and < 0.01/10^6, representing a more than 1000-fold difference in incidence. Overall, sarcomas are considered rare cancers, but the most of the individual subtypes are in fact extremely rare or ultra-rare. Thus, the study may be useful to complete the list of the 56 ultra-rare subtypes detected in the consensus. Table 2 shows the subtypes considered ultra-rare according to the established criterion of "incidence of approximately ≤ 1/million".

Ultra-rare sarcomas pose great challenges for diagnosis (around 20% of all sarcomas misclassified outside reference centers), for understanding disease biology and for generating clinical evidence to support new drug discovery and development[1]. This also leads to important difficulties to achieve formal authorization for novel therapies by regulatory agencies. Therefore, off-label use of medication is often the only way to access active treatments for these patients[1].

Correspondence:
Jean-Yves Blay
E-mail: jean-yves.blay@lyon.unicancer.fr

Table 1. *List of ultra-rare soft-tissue sarcomas identified based on incidence and of ultra-rare soft-tissue sarcomas identified on expert consensus only* (adapted from Stacchiotti et al., 2021[1])

Incidence Based on Population-Based Registries (RARECARENet EU, Asia, NETSARC)	WHO (Soft Tissue and Bone Tumors, Gynecologic, Head-and-neck, and Hematologic)[a]
Adult-type fibrosarcoma	
Alveolar rhabdomyosarcoma	
Alveolar soft part sarcoma	
Angiomatoid fibrous histiocytoma	
Clear cell sarcoma	
Desmoplastic small round cell tumor	
Ectomesenchymoma	
Embryonal rhabdomyosarcoma	
Embryonal sarcoma of the liver	High-grade *BCOR*-rearranged endometrial stromal sarcoma
Endometrial stromal sarcoma	High-grade *YWHAE*-rearranged endometrial stromal sarcoma
Endometrial stromal sarcoma, low grade	
Epithelioid sarcoma	
Extrarenal malignant rhabdoid tumour	
Extraskeletal	
Ewing sarcoma	
Extraskeletal myxoid chondrosarcoma	
Extraskeletal osteosarcoma	
Fibroblastic reticular cell tumor	
Follicular dendritic cell sarcoma	
Giant cell tumor of soft tissues	
Hemangioendothelioma, composite	
Hemangioendothelioma, epithelioid	
Hemangioendothelioma, pseudomyogenic	
Hemangioendothelioma, retiform	
Histiocytic sarcoma	
Infantile fibrosarcoma	
Inflammatory myofibroblastic tumor	Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma	Interdigitating dendritic cell sarcoma
Intimal sarcoma	
Langerhans cell sarcoma	
Low-grade fibromyxoid sarcoma	
Low-grade myofibroblastic sarcoma	
Malignant glomus tumor	
Malignant granular cell tumor	
Malignant myoepithelioma/myoepithelial carcinoma	
Malignant tenosynovial giant cell tumor	
Myxoinflammatory fibroblastic sarcoma	
Ossifying fibromyxoid tumor, malignant	
Papillary intralymphatic angioendothelioma	
PEComa, excluding non-epithelioid angiomyolipoma	
Phyllodes tumor, malignant	
Phosphaturic mesenchymal tumor, malignant	*CIC*-rearranged sarcoma
Pleomorphic liposarcoma	
Pleomorphic rhabdomyosarcoma	Round cell sarcoma with *EWSR1*-non-*ETS* fusions
	Sarcoma with *BCOR* genetic alterations
Round cell sarcoma/Ewing-like sarcoma	
Sclerosing epithelioid fibrosarcoma	Biphenotypic sinoanasal sarcoma
Spindle cell/sclerosing rhabdomyosarcoma	Inflammatory leiomyosarcoma
	Malignant melanotic nerve sheath tumor

[a]This column includes soft-tissue sarcoma histologic types not found in the population registries according to the 2020 WHO.
EU: European Union; NETSARC: French Clinical Reference Network for Soft Tissue and Visceral Sarcomas; PEComa: perivascular epithelial cell tumor; RARECARENet: Information Network on Rare Cancers; WHO: World Health Organization.

Table 2. *Ultra-rare sarcoma subtypes according to the criteria of incidence of approximately ≤ 1/million, in France in the period 2013-2016* (adapted from De Pinieux et al., 2021[2])

	2013	2014	2015	2016	Total	Incidence/10^6/year
Liposarcoma—round cell	18	16	13	7	54	0,205
Liposarcoma—pleomorphic	31	41	36	31	139	0.527
Lipomatous spindle cell/pleomorphic	0	1	0	0	1	0.004
Liposarcoma NOS	21	25	17	22	85	0.322
Liposarcoma-mixed type	0	0	1	1	2	0.008
Lipofibromatosis	3	0	5	0	8	0.030
Giant cell Fibroblastoma	2	4	4	1	11	0.042
Inflammatory myofibroblastic tumor	32	39	33	41	145	0.549
Low-grade Myofibroblastic Sarcoma	3	5	3	2	13	0.049
Myxoinflammatory Fibroblastic Sarcoma	6	6	6	5	23	0.087
Infantile fibrosarcoma	3	2	1	4	10	0.038
Adult-type fibrosarcoma	11	4	9	4	28	0.106
Low-grade fibromyxoid sarcoma	33	30	35	38	136	0.515
Sclerosing epithelioid fibrosarcoma	8	11	10	12	41	0.155
Intermediate fibrohistiocytic tumors (NOS)	0	0	2	3	5	0.019
Malignant tenosynovial giant cell tum	1	0	0	1	2	0.008
Plexiform fibrohistiocytic tumors	7	7	9	6	29	0.110
Giant cell tumor of soft tissue	21	9	26	14	70	0.265
Retiform hemangioendothelioma	1	3	3	2	9	0.034
Papillary intralymphatic angioendothelioma	0	0	0	1	1	0.004
Composite hemangioendothelioma	1	1	1	0	3	0.011
Kaposiform hemangioendothelioma	1	1	1	1	4	0.015
Pseudomyogenic hemangioendothelioma	1	3	0	2	6	0.023
Epithelioid hemangioendothelioma	27	20	30	23	100	0.379
Intermediate vascular tumors (NOS)	0	1	2	3	6	0.023
Pericytic (perivascular) tumors	4	4	1	1	10	0.038
SM tumor of undetermined malignancy	20	47	23	32	122	0.462
Metastatic leiomyoma	0	0	0	2	2	0.008
Embryonal RMS	50	45	60	34	189	0.716
Alveolar RMS	27	36	35	25	123	0.466
Pleomorphic RMS	28	38	42	36	144	0.545
Sclerosing RMS	2	3	3	3	11	0.042
Spindle cell RMS	13	8	9	9	39	0.148
Adult spindle cell RMS	0	0	1	4	5	0.019

(Continues)

Table 2. *Ultra-rare sarcoma subtypes according to the criteria of incidence of approximately ≤ 1/million, in France in the period 2013-2016* (adapted from De Pinieux et al., 2021[2]) (continued)

	2013	2014	2015	2016	Total	Incidence/10^6/year
RMS NOS	21	25	23	19	88	0.333
Ectomesenchymoma: Mal. mesenchymoma	4	2	0	3	9	0.034
Extraskeletal osteosarcoma	25	25	32	14	96	0.364
MPNST—epithelioid type	0	2	1	3	6	0.023
MPNST—usual type	36	7	14	28	85	0.322
Malignant peripheral nerve sheath tumor	36	55	47	35	173	0.655
Malignant Triton tumor	0	2	3	5	10	0.038
Malignant granular cell tumor	3	2	4	0	9	0.034
Malignant perineurioma	0	0	0	3	3	0.011
Angiomatoid fibrous histiocytoma	9	15	10	9	43	0.163
Ossifying fibromyxoid tumor	7	7	5	13	32	0.121
Myoepithelioma, myoepithelial carcinoma, and mixed tumor	31	26	18	18	93	0.353
Hemosiderotic fibrolipomatous tumor	0	2	0	7	9	0.034
Phosphaturic mesenchymal tumor	0	1	2	2	5	0.019
Epithelioid sarcoma (all)	29	30	28	33	120	0.455
Alveolar soft part sarcoma	10	7	8	6	31	0.117
Clear cell sarcoma of soft tissue	13	16	26	16	71	0.269
Extraskeletal myxoid chondrosarcoma	15	12	20	11	58	0.220
Desmoplastic small round cell tumor	14	9	12	17	52	0.197
Extrarenal rhabdoid tumor	6	13	16	16	51	0.193
SMARCA4-deficient thoracic sarcoma	0	0	6	9	15	0.057
PEComa, including angiomyolipoma	13	27	15	29	86	0.326
Intimal sarcoma	14	12	11	9	46	0.174
Low grade sinonasal sarcoma	2	0	0	3	5	0.019
Melanotic neuroectodermal tumor of infancy	0	0	0	1	1	0.004
Phyllodes sarcoma	32	25	46	35	138	0.523
Tumors of intermediate malignancy (NOS)	7	15	13	17	52	0.197

Specific ultra-rare subtypes and their treatment

Each ultra-rare sarcoma subtype deserves to be specifically investigated and treated. However, frequently, they are poorly characterized with regard to epidemiology, biology, natural history, prognostic and predictive factors, and sensitivity to standard treatments[1]. This leads to lack of specific robust data to choose the optimal treatment for ultra-rare STS with very few exceptions[1].

Due to this wide variety of extra-rare tumor subtypes, this special issue aims to define some of them in more detail based on the available evidence, complemented by real clinical cases.

Extraskeletal myxoid chondrosarcoma

Extraskeletal myxoid chondrosarcoma (EMC) is an ultra-rare sarcoma subtype with an incidence of < 1/10^6 person-years[3,4]. It is most common in adult males in their 50s, being very rare in children and adolescents. Most EMC occurs in the deep soft tissue of the proximal extremities and shoulder girdle, most commonly in the thigh. At present, EMC is classified as a mesenchymal tumor of uncertain differentiation[3]. This disease is not associated with cartilaginous differentiation and is distinguished from other soft-tissue sarcomas by multiple well-defined reciprocal chromosomal translocations involving the Nuclear Receptor Subfamily 4 Group A (NR4A3) gene[3,4].

Its initial symptomatology will depend on the region of onset, although it frequently presents as a large and deep soft-tissue mass that is accompanied by pain and can sometimes cause functional impairment[3].

When imaging tests are performed, a low-density lesion is usually seen on computed tomography (CT), while magnetic resonance imaging (MRI) shows a hyperintense signal with a hypotensive lesion in the internal septa, T2-weighted.[3]

The most common metastases of this tumor are in the lung. However, they can also be extra-pulmonary, with lymph node involvement being observed more frequently than in other soft-tissue sarcoma subtypes[3].

The standard treatment in cases with localized disease is wide local excision with negative microscopic margins, although recurrence rates after surgery are between 35% and 50% at 5 years[3,4]. Although data on the use of adjuvant or neoadjuvant radiotherapy or chemotherapy are not definitive, the general recommendations made for soft-tissue sarcoma are applicable to EMC[3,4]. In this regard, the 2021 ESMO guidelines indicate that wide excision and RT are the standard treatment of high-grade (G2-3) lesions[5]. They also indicate that adjuvant/neoadjuvant anthracycline plus ifosfamide chemotherapy for at least three cycles can be proposed to patients at high risk of death[5].

The metastasis rate observed after radical surgery in EMC ranges from 25-50%, although the survival rate is prolonged, even in the presence of metastatic disease[3]. Patients with non-resectable disease and metastases as well as evidence of disease progression should be treated with systemic therapy. As with neoadjuvant therapy, the recommendations of the 2021 ESMO guidelines on sarcoma treatment are followed, being anthracycline-based therapy the standard first-line treatment[5].

A retrospective study was conducted with data from 59 patients with EMC[6]. Twenty patients received chemotherapy for metastatic disease; best response was partial response with clinical benefit in 50% of patients. An anthracycline-based regimen was administered as first-line in 11 patients, with an overall control rate with anthracyclines of 60%. Fourteen patients received second-line treatment with a control rate of 46.1%. Three of these patients were treated with anthracyclines and did not obtain any benefit. However, another three patients were treated with trabectedin, and two of them had disease stabilization as best response, achieving an overall disease control rate of 66%. The study adds evidence to the poor performance of anthracycline-based chemotherapy, which was not associated with better outcomes, yet the use of trabectedin translated in overall fair disease control rates.

Recently, the Italian Sarcoma Group (ISG) conducted a multicenter, retrospective TrObs study in 512 pre-treated patients with advanced multiple sarcoma histology treated with trabectedin. A *post hoc* analysis was carried out among patients with ultra-rare and other rare sarcomas including 36 patients. Regarding the three patients with EMC, two of them had disease stabilization, representing a disease control rate of 66.7%. Consistent with the control rate reported in the previous study, the use of trabectedin in patients with multiple histotypes of ultra-rare sarcoma was confirmed with a manageable safety profile[7].

In addition, a randomized Phase 2 study in patients with translocation-related sarcomas unresponsive or intolerable to standard chemotherapy showed clinical benefit of trabectedin compared with best supportive care (BSC). A sub-analysis was performed in patients with EMC and mesenchymal chondrosarcoma (MCS)[8]. The trabectedin-treated group included five patients with EMC and MCS and the BSC group included three patients with MCS. In the five subjects of the trabectedin group, the median total number of trabectedin cycles was 10.0 (range, 8-22).The median PFS of the subjects with EMCS and MCS was 12.5 months (95% CI: 7.4–Not reached) in the trabectedin group, while 1.0 months (95% CI: 0.3-1.0 months) in MCS subjects of the BSC group. The 6-month progression-free rate (PFR) was 100 % in the trabectedin group. Median overall survival of EMCS and MCS subjects in the trabectedin group was 26.4 months (range, 10.4-26.4 months). The authors concluded that trabectedin is an important choice of treatment for patients with advanced EMCS or MCS who failed or were intolerable to standard chemotherapy.

Desmoplastic small round cell tumor (DSRCT)

DSRCT has an incidence of approximately 0.2-0.5 cases per million people. It affects primarily adolescents and young adults with a peak age of 20-24 years old, and it occurs predominantly in men[9]. It is characterized by a specific translocation involving chromosomes 11 and 22 (p13:q12) which is considered pathognomonic and whose detection is necessary for definitive diagnosis[9,10].

The clinical presentation of most patients is non-specific, with abdominal pain, bloating, weight loss, and alterations in bowel habits[10,11]. In these cases, the time interval from the onset of symptoms to the first medical consultation varies between 0 and 6 months[11].

DSRCT is usually presented as multiple peritoneal soft-tissue masses and in these cases, the appearance of the tumor may cause symptoms of bowel, ureter, or bile duct obstruction[11]. Approximately 60% of patients initially present with extra-abdominal metastases[9], commonly in liver (35-50%), followed by lymph node (thoracic, retroperitoneal, and inguinal), lung and bones[11], and the prognosis is poor, with a reported median OS of < 3 years and with long-term, disease-free survival unlikely to be achieved[9].

Since the tumor is frequently detected at an inoperable stage, complete resection is not feasible in many cases[9]. Favorable initial responses to combination chemotherapy, such as alkylating agent-based regimens, are not durable. A multimodal approach including combination chemotherapy, aggressive surgical resection, radiotherapy, and hyperthermic intraperitoneal chemotherapy (HIPEC) has been reported with clinical benefit[9].

A recent study also showed interesting results combining irinotecan, temozolomide, and bevacizumab, showing a 3-year OS of 61%[9]. Pazopanib resulted in a DCR of 78% and a median PFS of 9.2 months[9] and trabectedin showed a durable response with a partial response maintained in two patients after 48 and 36 months from treatment start[12]. The benefit of immunotherapy has rarely been reported, although several clinical trials are in progress[9].

Sclerosing epithelioid fibrosarcoma (SEF)

SEF is a rare form of soft-tissue sarcoma that is distinguished from other types of fibrosarcoma by its slow growth[13].

Its onset is more frequent in the fifth decade of life and there seems to be no gender difference in its prevalence[14,15].

Morphologically, it is characterized by the presence of clusters or cords of epithelioid neoplastic cells immersed in a sclerotic extracellular matrix[13,14]. It is a malignant neoplasm with high local recurrence rates (approximately 50% of cases) with a median recurrence

time of 3.5 years[13,14]. Distant metastases occur in 43-86% of cases with a median time to onset of 3-14 years[13,14]. The most frequent sites for metastasis are the lungs, followed by bone, lymph nodes and pleura[13,14].

It usually presents as a deep intramuscular mass located in the lower limbs, pelvic girdle, trunk, upper limbs, and in the head-and-neck area[14,15]. Patients report a painless mass in the lower limbs for several months of evolution, while the location of the tumor in other anatomical areas will produce signs and symptoms related to the mass effect in the area of occurrence[15].

Cytoplasmic immunohistochemical expression of mucin 4 (MUC4) is sensitive and specific for SEF[14,15].

The main differential diagnosis is done with metastatic carcinoma, benign soft-tissue tumors and high-grade sarcomas[13,15].

Surgical resection remains the standard treatment for SEF, with wide surgical resection being the most effective strategy. The benefit of radiotherapy remains in doubt and is performed only in patients at risk for recurrence or metastasis such as margin positivity, tumor location, and tumor size. The efficiency of adjuvant therapy in the control of SEF is not yet demonstrated. Chemotherapy is reserved for patients whose tumors recur locally or spread to distant[16]. Regular and long-term follow-up is recommended, since, as mentioned above, recurrences or distant metastases may appear after several years[13].

Due largely to its rarity and having only relatively recently being recognized as a distinct diagnostic entity, SEF is associated with a limited published literature. Reports of systemic treatment outcomes have been mostly limited to a handful of case reports where patients were treated with doxorubicin-based therapy. A retrospective search of a referral center database identified 13 patients with SEF who were treated between 1990 and 2017[17]. In total, 12 (92.3%) patients developed metastatic disease of which 10 died of disease, one was lost to follow-up and one had commenced palliative treatment. Among the 10 patients with metastatic disease, seven received palliative chemotherapy resulting partial response in one patient, stable disease in three patients and progressive disease in three patients. Two of 13 patients were treated with adjuvant chemotherapy, receiving six cycles of liposomal doxorubicin and one cycle of doxorubicin, respectively, with a metastasis-free survival of 28.2 and 7.1 months, respectively[17].

There have been case reports of patients with SEF treated with trabectedin, including one patient who was part of a post-marketing study conducted in Japan to assess the efficacy and safety of trabectedin. A median PFS of 6.3 months and OS of 16.6 months was observed[18].

Conclusions

Close scrutiny and knowledge of each type of ultra-rare sarcoma are necessary, despite representing major challenges for diagnosis, understanding of its biology, generation of evidence, and obtaining formal authorizations. For that, a sustainable global collaborative effort is required that allows the sarcoma research community to collaborate on a global scale, pharmaceutical companies to value partnerships with academia, and regulatory bodies to listen to disease-based communities, involving researchers and patient advocates.

References

1. Stacchiotti S, Frezza AM, Blay JY, Baldini EH, Bonvalot S, Bovée JV, et al. Ultra-rare sarcomas: a consensus paper from the connective tissue oncology society community of experts on the incidence threshold and the list of entities. Cancer. 2021;127:2934-42.
2. De Pinieux G, Karanian M, Le Loarer F, Le Guellec S, Chabaud S, Terrier P, et al. (2021). Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PLoS One. 2021;16:e0246958.
3. Stacchiotti S, Baldi GG, Morosi C, Gronchi A, Maestro R. Extraskeletal myxoid chondrosarcoma: state of the art and current research on biology and clinical management. Cancers (Basel). 2020;12:2703.
4. Brown JM, Rakoczy K, Pretell-Mazzini J. Extraskeletal myxoid chondrosarcoma: clinical features and overall survival. Cancer Treat Res Commun. 2022;31:100530.
5. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:1348-65.

6. Chiusole B, Le Cesne A, Rastrelli M, Maruzzo M, Lorenzi M, Cappellesso R, et al. Extraskeletal myxoid chondrosarcoma: clinical and molecular characteristics and outcomes of patients treated at two institutions. Front Oncol. 2020;10:828.
7. Palmerini E, Sanfilippo R, Grignani G, Buonadonna A, Romanini A, Badalamenti G, et al. Ultra-rare and Other Rare Advanced Sarcoma Treated with Trabectedin: a Post-Hoc Analysis of a Non-Interventional, Retrospective, Multicenter Study of the Italian Sarcoma Group. Abstract ID:1819054. Poster 253 Presented at CTOS 2021 Virtual Annual Meeting; 2021.
8. Morioka H, Takahashi S, Araki N, Sugiura H, Ueda T, Takahashi M, et al. Results of sub-analysis of a phase 2 study on trabectedin treatment for extraskeletal myxoid chondrosarcoma and mesenchymal chondrosarcoma. BMC Cancer. 2016;16:479.
9. Jeong H, Hong YS, Kim YH, Kim CW, Song SY, Song JS, et al. The role and clinical effectiveness of multiline chemotherapy in advanced desmoplastic small round cell tumor. Clin Med Insights Oncol. 2021; 15:1179554920987107.
10. Espinosa-Cotton M, Cheung NV. Immunotherapy and radioimmunotherapy for desmoplastic small round cell tumor. Front Oncol. 2021; 11:772862.
11. Hendricks A, Boerner K, Germer CT, Wiegering A. Desmoplastic small round cell tumors: a review with focus on clinical management and therapeutic options. Cancer Treat Rev. 2021;93:102140.
12. Stacchiotti S, Frezza AM, Gronchi A, Pasquali S, Radaelli S, Fiore M, et al. Trabectedin (T) in desmoplastic small round cell tumor (DSRCT): report of its effect in 3 relapsed patients (pts) and the comparison of different regimens in a patient-derived xenograft (PDX) model. J Clin Oncol. 2021;39:e23553.
13. Yahyaoui M, Benhammou M, Aharram S, Amghar J, Sadougui M, Agoumi O, et al. Sclerosing epithelioid fibrosarcoma: rare and serious. Pan Afr Med J. 2020;36:131.
14. Righi A, Pacheco M, Pipola V, Gambarotti M, Benini S, Sbaraglia M, et al. Primary sclerosing epithelioid fibrosarcoma of the spine: a single-institution experience. Histopathology. 2021;78:976-86.
15. Murshed KA, Al-Bozom I, Ammar A. Sclerosing epithelioid fibrosarcoma: in-depth review of a genetically heterogeneous tumor. APMIS. 2021;129:455-60.
16. Khezami K, Gharbi A, Chabaane M, Bennour MA, Nouri H. Primary sclerosing epithelioid fibrosarcoma presenting as lombosciatic syndrome: case report and literature review. Int J Surg Case Rep. 2021;80:105657.
17. Chew W, Benson C, Thway K, Hayes A, Miah A, Zaidi S, et al. Clinical characteristics and efficacy of chemotherapy in sclerosing epithelioid fibrosarcoma. Med Oncol. 2018;35:138.
18. Kobayashi H, Iwata S, Wakamatsu T, Hayakawa K, Yonemoto T, Wasa J, et al. Efficacy and safety of trabectedin for patients with unresectable and relapsed soft-tissue sarcoma in Japan: A Japanese musculoskeletal oncology group study. Cancer. 2020;126:1253-63.

Clinical case 1

Extraskeletal myxoid condrosarcoma: A clinical case at Hospital Sant Pau

Ana Sebio

Department of Oncology, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

A 68-year-old male with the previous history of hypercholesterolemia treated with simvastatin and untreated benign prostate hyperplasia.

Patient was diagnosed in 1998 with localized extraskeletal myxoid chondrosarcoma (EMC) EWSR1 traslocated by FISH, measuring 6.5 cm located in the left triceps. He was treated with surgery in December 1998 achieving negative margins (R0) and received adjuvant radiotherapy with a total of 64 Gys. Patient was followed for 15 years with no evidence of disease and was discharged in 2013.

In December 2016, after progressive dyspnea symptoms, he was diagnosed at another hospital with a thoracic relapse showing a left axillary mass, an irregular and concentric pleural thickening predominantly in the left hemithorax and multiple subcentimeter lung nodes compatible with lung metastasis (Fig. 1). A fine needly aspiration of the axillary mass was performed showing malignant cells and revision at our hospital showed immunohistochemistry compatible with EMC. He received first-line doxorubicin with a total of six cycles (from January 2016 to April 2016) achieving stable disease. In subsequent scans our patient maintained stable disease, but he complained of pain and limited mobility of the left upper extremity due to the axillary mass. In July 2018, the axillary mass was completely removed, and pathology showed an 8 × 4 × 3 cm mass marginally removed.

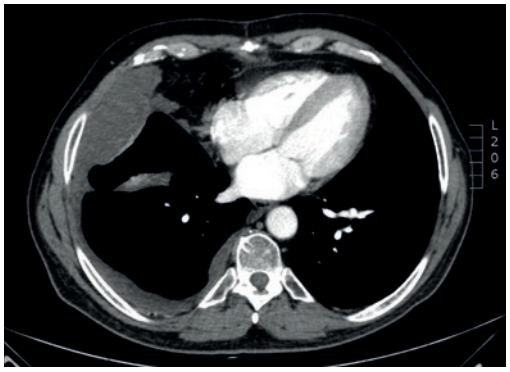

Figure 1. *Late relapse.*

In February 2019, the patient presented with progressive disease with an important increased in the pleural thickening and increased in the size of the lung nodes. He was started on pazopanib 800 mg OD but computed tomography (CT) scan after three cycles showed progressive disease and the patient was clinically symptomatic with increasing dyspnea.

In June 2019, treatment with trabectedin was initiated (Fig. 2) and after three cycles, CT scan showed partial response (Fig. 3).

Correspondence:
Ana Sebio
E-mail: asebio@santpau.cat

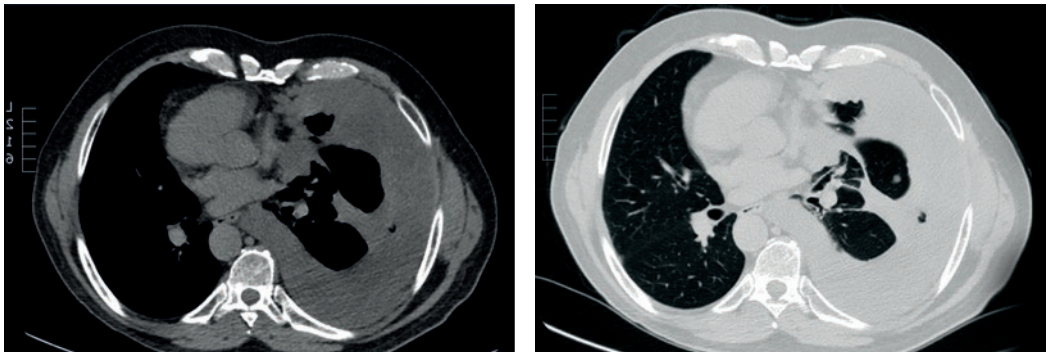

Figure 2. *Baseline trabectedin.*

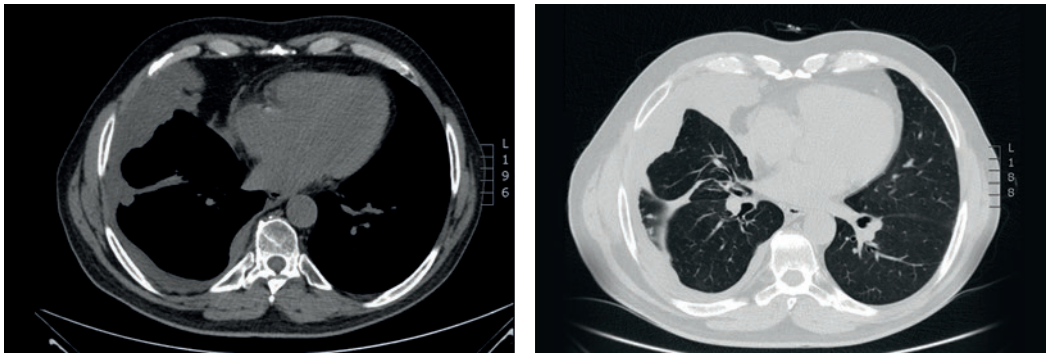

Figure 3. *Trabectedin response after 3 cycles.*

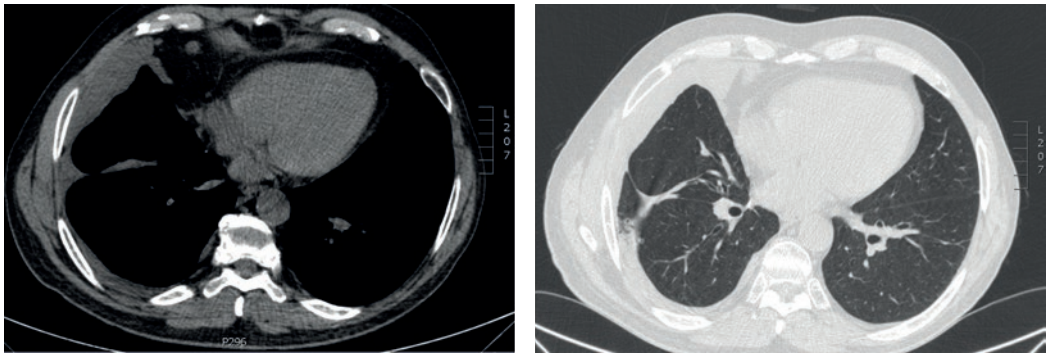

Figure 4. *Enhanced response to trabectedin observed in subsequent CT scans.*

In subsequent scans, an enhanced response to trabectedin was observed (Fig. 4) and patient's symptoms improved. He continued trabectedin having required one dose reduction due to hematological toxicity (anemia and neutropenia, both grade 2). Trabectedin was stopped after 20 cycles after discussing options with the patient and his family. He

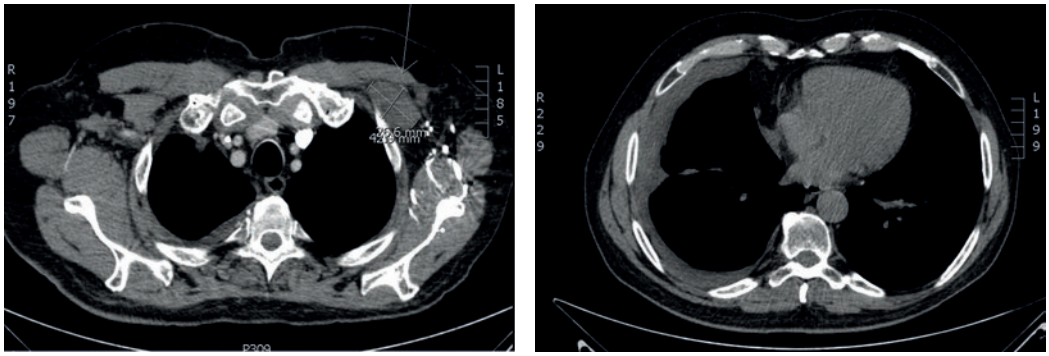

Figure 5. *Baseline sunitinib-nivolumab.*

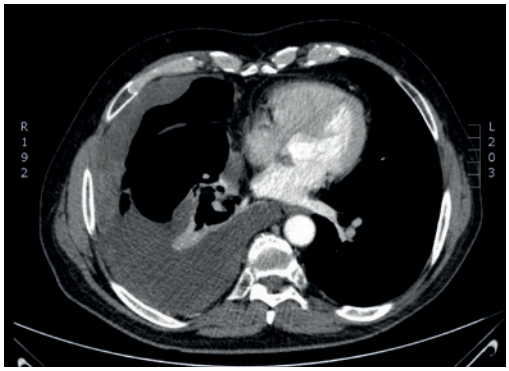

Figure 6. *Progresive disease sunitinib-nivolumab. Baseline trabectedin rechallenge.*

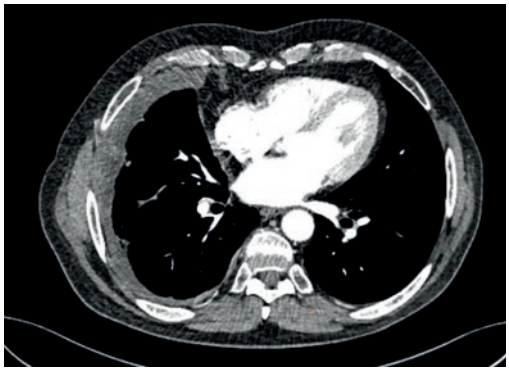

Figure 7. *Trabectedin rechallenge response.*

continued follow-up until disease pleuropulmonar progression was observed as well as a new retropectoral mass in a scan performed in August 2021 (progression-free survival 27 months) (Fig. 5).

At that time, the patient was enrolled in a clinical trial (Inmunosarc2-GEIS 52 NCT03277924) and received treatment with sunitinib and nivolumab. Before the scheduled response evaluation scan was performed, he presented with symptomatic dyspnea and a CT scan was performed (Fig. 6) showing clear pleural progressive disease, so the study medication was discontinued.

In October 2021, rechallenge with trabectedin was initiated and led to a new partial response after four cycles of treatment (Fig. 7). In April 2022, treatment was discontinued after 9 cycles, despite having previously reduced the dose due to grade 3 anemia. Latest CT scan was performed in June 2022 showing maintained response.

Discussion

EMC is an ultrarare type of sarcoma typically arising in the extremities and limb girdles that is characterized by a specific translocation involving NR4A3 and EWRS1 in the majority of cases[1]. Standard treatment in localized disease is surgical resection ± neo or adjuvant radiotherapy[2]. Long-term survival is long but the risk of developing metastatic disease if high[3].

In metastatic disease, this entity is considered to be chemo-resistant, but some studies have found activity of chemotherapy for EMC[4].

For this reason, the patient was treated first with standard doxorubicin monotherapy achieving stable disease that lasted for more than 3 years.

After disease progression, the chosen second line was pazopanib. Pazopanib was evaluated by the Spanish, Italian, and French sarcoma groups in a non-randomized Phase II trial. A total of 26 patients were treated with pazopanib at the standard dose and with a median follow-up of 27 months, 18% of the patients had a RECIST 1.1 objective response[5]. Our patient had a rapid progressive disease on pazopanib and derived no benefit from this treatment.

Trabectedin third-line was based on the previous publications suggesting benefit of trabectedin in translocation-related sarcomas[6] and specifically also in EMC[7]. The patient achieved RECIST 1.1 partial response which lasted more than 2 years. Despite the results of the French sarcoma group T-DIS trial in which it was shown that continuing trabectedin after six initial cycles was better regarding 6-month progression-free survival than a stop and go approach[8], it was decided to stop treatment due to hematological toxicity and patient preference.

When disease progression was detected, the patient was included in a sunitinib plus nivolumab trial which permitted prior treatment with pazopanib. However, as happed with the prior antiogangiogenic therapy, and despite the addition of nivolumab, the patient had a rapid progression. Trabectedin rechallenge was started and the patient achieved for second time a partial response. Rechallenge with trabectedin was explored in the T-DIS trial showing that trabectedin retains activity after a treatment break[9]. Treatment had to be stopped after nine cycles due to hematological toxicity and currently the patient is on treatment break. It is planned to consider rechallenge with trabectedin on progression.

References

1. International Agency for Research on Cancer. World Health Organization Classification of Tumours Editorial Board. Soft tissue and bone tumours. Lyon (France): International Agency for Research on Cancer; 2020.
2. Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:1348-65.
3. Chiusole B, Le Cesne A, Rastrelli M, Maruzzo M, Lorenzi M, Cappellesso R, et al. Extraskeletal myxoid chondrosarcoma: clinical and molecular characteristics and outcomes of patients treated at two institutions. Front Oncol. 2020;10:828.
4. Stacchiotti S, Baldi GG, Morosi C, Gronchi A, Maestro R. Extraskeletal myxoid chondrosarcoma: state of the art and current research on biology and clinical management. Cancers (Basel). 2020;12:2703.
5. Stacchiotti S, Ferrari S, Redondo A, Hindi N, Palmerini E, Vaz Salgado MA, et al. Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, Phase 2 trial. Lancet Oncol. 2019;20:1252-62.
6. Le Cesne A, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, et al. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. Eur J Cancer. 2012;48:3036-44.
7. Morioka H, Takahashi S, Araki N, Sugiura H, Ueda T, Takahashi M, et al. Results of sub-analysis of a Phase 2 study on trabectedin treatment for extraskeletal myxoid chondrosarcoma and mesenchymal chondrosarcoma. BMC Cancer. 2016;16:479.
8. Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised Phase 2 trial. Lancet Oncol. 2015;16:312-9.
9. Kotecki N, Le Cesne A, Tresch-Bruneel E, Ray-Coquard I, Chevreau C, Bertucci F, et al. Impact of trabectedin interruption and subsequent rechallenge on progression in patients with advanced soft tissue sarcoma: long-term follow-up of the T-DIS trial. Am J Clin Oncol. 2018; 41:1094-100.

Clinical case 2

Prolonged survival of a patient with desmoplastic small round cell tumor

Rosa Álvarez[1], Mar Galera López[1], Marta Arregui[1], Ana Álvarez[2], Raphael A. González Crisostomo[3], Antonio Calles[1], David S. Juliao Caamaño[1], Natalia Gutiérrez Alonso[1], Enrique de Miguel[4], and Carolina Agra[5]*

[1]Department of Medical Oncology, Hospital Universitario Gregorio Marañón, Madrid, Spain; [2]Department of Radiation Oncology, Hospital Universitario Gregorio Marañón, Madrid, Spain; [3]De La Salle Medical and Health Sciences Institute, Damariñas, Cavite; [4]Department of Radiology, Hospital Universitario Gregorio Marañón, Madrid, Spain; [5]Department of Anatomic Pathology, Hospital Universitario Gregorio Marañón, Madrid, Spain

We present the case of a 34-year-old male patient who was diagnosed with Stage IV desmoplastic small round cell tumor (DSRCT), an aggressive disease with a poor prognosis. The patient received multiple lines of treatment achieving long-term survival with a prolonged response to trabectedin (T) for more than 1 year.

No toxic habits, no known allergies to medication, or any remarkable medical history.

No family history of cancer.

The patient presented with abdominal pain localized to the right hypochondrium in April 2018. Subsequently, he developed abdominal distention and low-grade fever predominantly in the afternoon. Hepatomegaly was noted on physical examination.

Diagnosis

A computed tomography (CT) scan (June 2018) performed at another medical center revealed a retroperitoneal mass with peritoneal carcinomatosis and multiple hepatic metastases. A liver biopsy was performed although a conclusive diagnosis was not reached.

The patient was referred to our hospital, a national reference center for sarcoma, in July 2018. A core needle liver biopsy was performed which led to the diagnosis of a desmoplastic small round cell tumor (Fig. 1A and B). Immunohistochemical (IHC) analysis was positive for Ep-CAM, Enolase, CD15, and Desmine, while negative for CD31, CD34, CD45, CD117, Synaptophysin, Cromogranine, Myogenin, Actin ML, and SOX10. The rate of cell proliferation with Ki67 was more than 90%.

The tumor demonstrated strong WT1 nuclear immunoreactivity (Fig. 2). It was later confirmed by fluorescence in situ hybridization that the tumor contained the characteristic translocation t(11;22) (p13;q12) EWSR1-WT1.

Treatment

The patient was admitted to our hospital with ECOG 2 performance status after symptoms worsened, to start systemic chemotherapy without delay.

Correspondence:
Rosa Álvarez
E-mail: rosa.alvarez.al@gmail.com

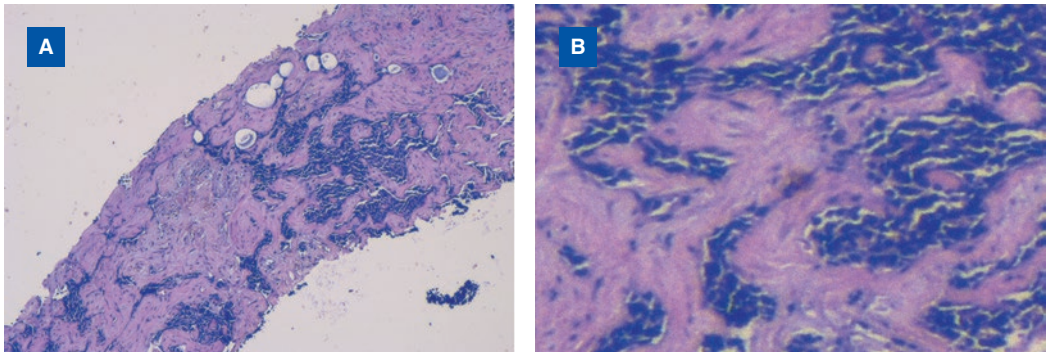

Figure 1. *Histologic images with Hematoxylin and Eosin staining (H and E).* ***A:*** *a neoplastic proliferation of mesenchymal lineage is observed. There are cords and nest structures on an intensely desmoplastic stroma. Occasionally, the cells are arranged around blood vessels.* ***B:*** *the neoplastic cells are round, small, and blue. They have indistinguishable cytoplasmic borders and scant cytoplasm. The nuclei are small, hyperchromatic, without evident nucleoli, and with isolated figures of mitosis (2/10HPF). The desmoplastic stroma is composed of fibroblasts and myofibroblasts on a poorly collagenized extracellular material, with myxoid areas. No areas of tumor necrosis are observed.*

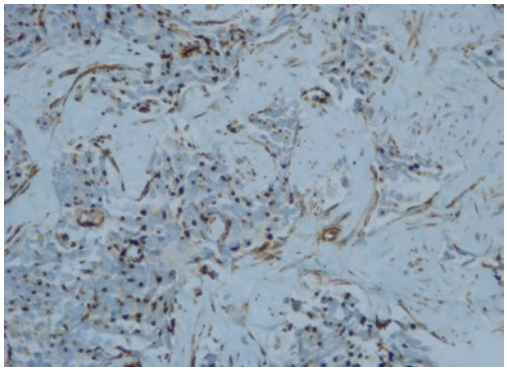

Figure 2. *Immunohistochemical staining is positive for WT-1. WT1 immunostaining using a polyclonal antibody directed against the WT1 part of the chimeric protein results from the characteristic translocation t(11;22) (p13;q12) EWSR1-WT1.*

First line

In August 2018, following port-a-cath placement, the patient started systemic chemotherapy according to the P6 protocol (seven cycles of VDC and IE).

First-line treatment with VDC (vincristine 0.67 mg/m^2 d1-3, doxorubicin 25 mg/m^2 d1-3, cyclophosphamide 2100 mg/m^2 d1-2 every 3 weeks) was initiated on the 8th of August. Although the patient presented with hematological toxicity (Grade 4 febrile neutropenia and Grade 4 thrombocytopenia), an improvement in the abdominal pain and low-grade fever was noted after the first cycle.

After three cycles, a partial response was observed on the CT scan (November 29, 2018). Due to the patient presenting with a major partial response and considering the possibility of surgical rescue, the patient was given VDC for five cycles. Despite chemotherapy dose reduction due to hematological toxicity, all cycles of chemotherapy were delayed.

Debulking surgery was finally ruled out after the assessment of the multidisciplinary tumor board, due to the extensive extra-peritoneal disease. In February 2019, IE (Ifosfamide 100 mg/m^2, Etoposide 1.8 mg/m^2 d1-5 every 3 weeks) was started. There were delays in chemotherapy administration due to the recurrence of hematological toxicity with Grade 4 thrombocytopenia. After two cycles, hepatic progression of the disease was observed on CT scan (April 11, 2019).

Second line

In April 2019, Irinotecan 20 mg/m^2 d1-5 and temozolamide 100 mg/m^2 d1-5 every 21 days

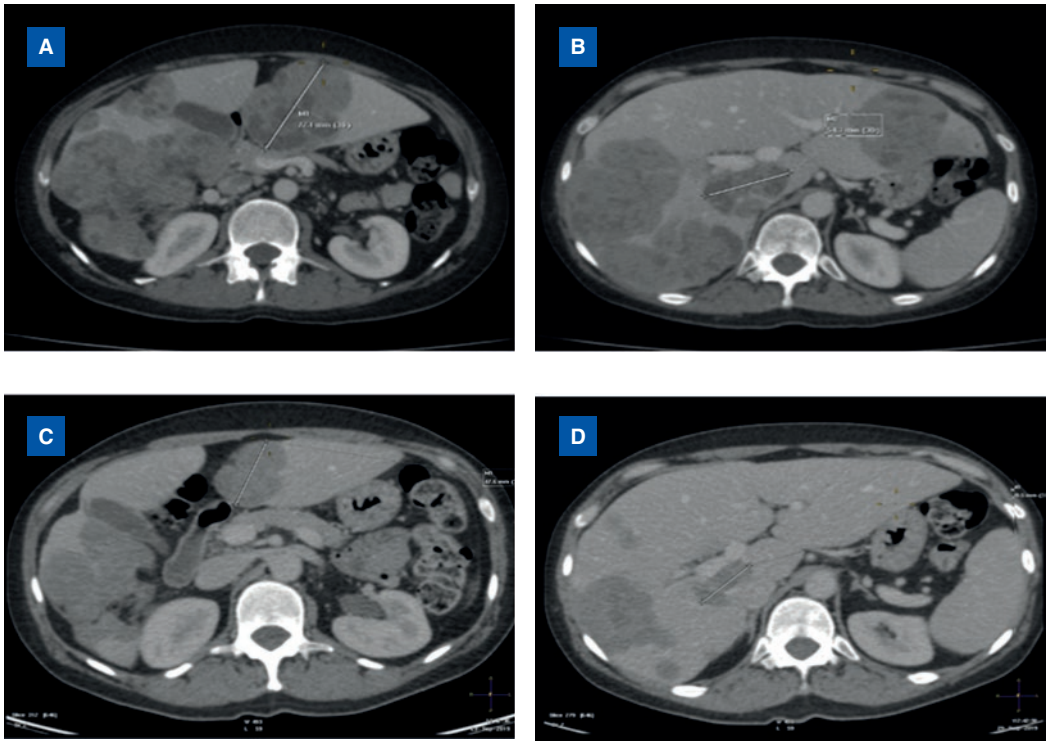

Figure 3. ***A and B:*** *hepatic disease before treatment with trabectedin.* ***C and D:*** *hepatic disease after response to trabectedin.*

were started. Hematological toxicity with thrombocytopenia was observed once again along with worsening abdominal pain. After three cycles, further hepatic and peritoneal progression of the disease was observed on CT scan (July 25, 2019).

Third line

In July 2019, a new line of treatment with trabectedin (1.5 mg/m^2) was started.

Despite the administration of three doses of recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) in the first cycle, the patient had hematological toxicity (Grade 4 febrile neutropenia and Grade 4 thrombocytopenia) which caused the delay of the next cycle for up to 3 weeks. The dose of trabectedin for the second cycle had to be decreased one level to 1.2 mg/m^2 and the dose of G-CSF was increased for 7 days.

After three cycles, the patient experienced an improvement in abdominal pain. The CT scan (September 29, 2019) (Fig. 3) demonstrated stabilization of the peritoneal disease and a major partial hepatic response.

The patient showed good tolerance to the treatment, but after a new episode of hematological toxicity (Grade 3 neutropenia and Grade 3 thrombocytopenia), the trabectedin dose was reduced by another level to 1 mg/m^2.

The subject was treated with nine cycles of trabectedin until March 2020, when a CT scan (March 24, 2020) revealed a progression of the pelvic implant despite a continuous response of the peritoneal and hepatic disease. On the assessment of the multidisciplinary tumor board, it was decided to continue trabectedin. Radiotherapy of the pelvic implant was initiated. The patient received 10 × 300 cGy (from April 22 to May 6, 2020) with good tolerance.

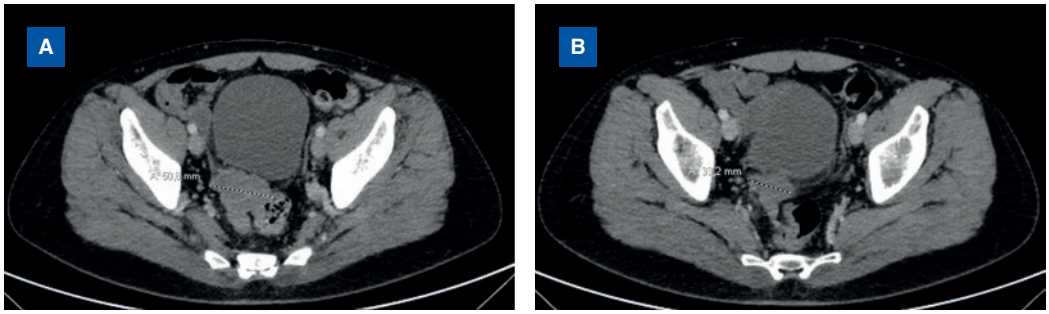

Figure 4. *Computed tomography scan:* ***A:*** *pelvic tumor implant after nine cycles of trabectedin and* ***B:*** *after radiotherapy of the pelvic implant.*

The following CT scan (June 2020) (Fig. 4) demonstrated a partial response of the pelvic implant, in addition to tumoral stability of peritoneal and hepatic disease.

The patient continued on trabectedin with 4-week intervals and pegfilgrastim for better hematological tolerance. After 15 cycles, hepatic progression was observed on CT scan (September 13, 2020) and treatment was stopped (Fig. 5).

Fourth line

In October 2020, pazopanib 800 mg once daily was started with excellent tolerance. Tumor stabilization was noted on the CT scan (December 22, 2020). Nevertheless, hepatic tumor progression was observed again in February 2021.

Fifth line

In March 2021, topotecan (0.75 mg/m^2/day, days 1-5) and cyclophosphamide (250 mg/m^2/day, days 1-5) every 3 weeks were started. The patient experienced hematological toxicity (predominantly grade 4 thrombocytopenia), as was observed with other lines, resulting in chemotherapy dose reductions. Following two cycles, a CT scan showed stabilization of the disease. The patient was given five cycles before the treatment was suspended due to hepatic and peritoneal tumor progression.

Sixth line

A new line of treatment with gemcitabine 900 mg/m^2 days 1 and 8 and docetaxel 75 mg/m^2 day 8 every 21 days was started in July 2021. Even though a partial response after three cycles was attained, the patient experienced significant hematological toxicity and multiple delays in the administration of the cycles. Treatment was stopped in December 2021 after seven cycles due to peritoneal progression.

Following lines of treatment

Vinorelbine 25 mg/m^2 on days 1 and 8 and daily oral cyclophosphamide 25 mg/m^2 (d1-28) every 28 days were administered as the seventh line of treatment (from December 28, 2021, to March 13, 2022). Following the third cycle, a new progression of the disease at hepatic, peritoneal, and pulmonary levels was observed.

In May 2022, dilatation of the biliary tract secondary to hepatic and ganglionar tumor infiltration was noted. Post-biliary drainage, an attempt of an eighth line of chemotherapy with high-dose ifosfamide was started. However, chemotherapy was interrupted after one cycle due to a lack of hepatic improvement and biliary sepsis.

At the latest follow-up in July 2022, the patient was under palliative symptomatic treatment at home.

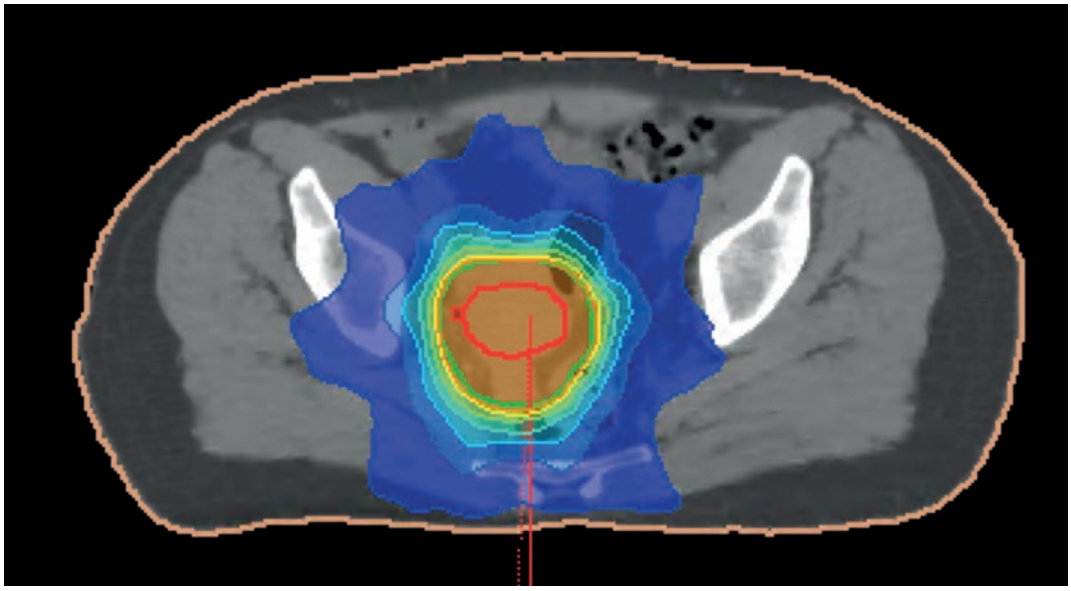

Figure 5. *Radiation therapy with VMAT, 10 fraction × 300 cGy.*

Discussion

We present a case of DSCRT, a rare sarcoma with a very poor prognosis without standard treatment after first-line chemotherapy progression, which had a significant prolonged response to trabectedin.

DSRCT is an aggressive tumor that predominantly occurs in young males, with an approximate incidence of 0.2-0.5 cases per million[1-3].

It typically presents with multiple peritoneal tumors, pelvic involvement, and often extraperitoneal metastatic disease[1-5].

Histologically, it is characterized by small round cells with small, hyperchromatic nuclei, and scant cytoplasm. They are arranged in nests and are surrounded by prominent stromal desmoplasia[5,6]. On immunohistochemistry, coexpression of epithelial (keratin and EMA), myogenic (desmin), neural (NSE and CD56), and mesenchymal (vimentin) markers are typical[5,7]. The nuclear expression of WT1 is characteristic. The presence of the EWRS1-WT1 translocation is seen in practically all cases[6,7].

Despite multimodal treatment approaches, the prognosis for DSRCT is extremely poor, with a reported median survival ranging from 17 to 25 months and a 5-year survival rate of 15-25%[6,8].

The optimal treatment for patients without extra-abdominal disease is multimodal therapy with intensive multi-agent chemotherapy and cytoreductive surgery[3,4,8-10]. Complete cytoreductive surgery is the only potentially curative treatment and the role of hyperthermic peritoneal perfusion with chemotherapy after cytoreduction remains unclear[10].

Although there is no standard chemotherapeutic treatment regimen, most are based on alkylating agents, similar to those for Ewing's sarcoma[1-4,11]. Even though a response to treatment is the norm, the duration of treatment is rarely prolonged and new drugs effective in this setting are urgently needed.

Trabectedin is a marine-derived agent, approved in Europe for the treatment of adult patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents[12,13]. Although it is a drug that has demonstrated activity in multiple histological subtypes, it is especially active in myxoid liposarcoma[14]. This histological subtype is characterized by the

expression of the oncogenic transcript FUS/CHOP and presents an overall response rate to trabectedin of 50% and a median PFS of 17 months[14]. Likewise, there are data on trabectedin in other sarcomas related to the presence of translocations[15,16].

The potential efficacy of trabectedin in DSRCT, a sarcoma with EWRS1-WT1 translocation, was first described by Lopez-Gonzalez et al. reporting the case of a patient who achieved a partial response with trabectedin as third-line treatment[17]. Since then, there have been several published cases describing its efficacy in this histologic subtype[18-21].

In this clinical case, the patient presented a striking and prolonged partial response, superior to those previously described in the literature. He had a local pelvic recurrence 8 months after starting trabectedin, treated with radiotherapy, and due to this approach, the disease was controlled for a period of more than 1 year.

With our experience, we support the hypothesis suggesting that trabectedin is active in DSRCT and that it was able to achieve meaningful symptomatic control thanks to the significant and prolonged response obtained, allowing the patient to have an overall survival of more than 4 years. Furthermore, tolerability was favorable, and dose adjustment easily controlled toxicity. Our results, together with data available in the literature, suggest that trabectedin is a potentially active treatment option to explore prospectively in the treatment of refractory DSRCT and, therefore, could be considered as a potential additional line of treatment in this disease.

References

1. Martínez-Trufero J, Cruz Jurado J, Hernández-León CN, Correa R, Asencio JM, Bernabeu D, et al. Uncommon and peculiar soft tissue sarcomas: multidisciplinary review and practical recommendations. Spanish group for sarcoma research (GEIS-GROUP). Part II. Cancer Treat Rev. 2021;99:102260.
2. Honore C, Delhorme JB, Nassif E, Faron M, Ferron G, Bompas E, et al. Can we cure patients with abdominal desmoplastic small round cell tumor? Results of a retrospective multicentric study on 100 patients. Surg Oncol. 2019;29:107-12.
3. Bulbul A, Fahy BN, Xiu J, Rashad S, Mustafa A, Husain H, et al. Desmoplastic small round blue cell tumor: a review of treatment and potential therapeutic genomic alterations. Sarcoma. 2017;2017:1278268.
4. Hayes-Jordan A, LaQuaglia MP, Modak S. Management of desmoplastic small round cell tumor. Semin Pediatr Surg. 2016;25:299-304.
5. Thway K, Noujaim J, Zaidi S, Miah AB, Benson C, Messiou C, et al. Desmoplastic small round cell tumor: pathology, genetics, and potential therapeutic strategies. Int J Surg Pathol. 2016;24:672-84.
6. Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F. Pathology and genetics of tumours of soft tissue and bone. In: World Health Organization Classification of Tumors. 4th ed. Lyon: IARC Press; 2013.
7. De Alava E, Marcilla D. Birth, and evolution of the desmoplastic small round-cell tumor. Semin Diagn Pathol. 2016;33:254-61.
8. Lal DR, Su WT, Wolden SL, Loh KC, Modak S, La Quaglia MP. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005;40:251-5.
9. Subbiah V, Lamhamedi-Cherradi SE, Cuglievan B, Menegaz BA, Camacho P, Huh W, et al. Multimodality treatment of desmoplastic small round cell tumor: chemotherapy and complete cytoreductive surgery improve patient survival. Clin Cancer Res. 2018;24:4865-73.
10. Hayes-Jordan A, Green HL, Lin H, Owusu-Agyemang P, Fitzgerald N, Arunkumar R, et al. Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor. Ann Surg Oncol. 2014;21:220-4.
11. Kushner BH, LaQuaglia MP, Wollner N, Meyers PA, Lindsley KL, Ghavimi F, et al. Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol. 1996;14:1526-3.
12. Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized Phase II study of two different schedules. J Clin Oncol. 2009;27:4188-96.
13. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a Phase III randomized multicenter clinical trial. J Clin Oncol. 2016;34:786-93.
14. Grosso F, Sanfilippo R, Virdis E, Piovesan C, Collini P, Dileo P, et al. Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series. Ann Oncol. 2009;20:1439-44.
15. Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomized, open-label, Phase 2 study. Lancet Oncol. 2015;16:406-16.
16. Blay JY, Leahy MG, Nguyen BB, Patel SR, Hohenberger P, Santoro A, et al. Randomised Phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer. 2014;50:1137-47.
17. López-González A, Cantos B, Tejerina E, Provencio M. Activity of trabectidin in desmoplastic small round cell tumor. Med Oncol. 2011; 28:S644-6.
18. Verret B, Honore C, Dumont S, Terrier P, Adam J, Cavalcanti A, et al. Trabectedin in advanced desmoplastic round cell tumors: a retrospective single-center series. Anticancer Drugs. 2017;28:116-9.
19. Ferrari A, Chiaravalli S, Bergamaschi L, Nigro O, Livellara V, Sironi G, et al. Trabectedin-irinotecan, a potentially promising combination in relapsed desmoplastic small round cell tumor: report of two cases. J Chemother. 2022;26:1-5.
20. Frezza AM, Whelan JS, Dileo P. Trabectedin for desmoplastic small round cell tumors: a possible treatment option? Clin Sarcoma Res. 2014;4:3.
21. Palmerini E, Sanfilippo R, Grignani G, Buonadonna A, Romanini A, Badalamenti G, et al. Ultra-rare and Other Rare Advanced Sarcoma Treated with Trabectedin: a Post-Hoc Analysis of a Non-Interventional, Retrospective, Multicenter Study of the Italian Sarcoma Group. Abstract ID:1819054. Poster 253 Presented at CTOS 2021 Virtual Annual Meeting; 2021.

Clinical case 3

Prolonged clinical benefit in advanced line sclerosing epithelioid fibrosarcoma and spinal cord compression

Fernando Gálvez Montosa and Javier Requena Aguilar*

UGC Oncología Médica, Hospital Universitario de Jaén, Jaén, Spain

A 47-year-old patient with no history of interest consulted his primary care doctor for a lump in the right buttock that had grown progressively in the past 3 months, which was painful when sitting down. On examination, a hard lesion with little mobility of about 6 cm was noticed. An MRI was requested, which showed an 8.8 cm lesion in the thickness of the gluteus maximus muscle with radiological characteristics of aggressiveness, suggestive of a sarcomatous lesion (Fig. 1).

The case was presented in a multidisciplinary committee, and it was decided to take a biopsy, which showed a mesenchymal lesion morphologically compatible with sclerosing epithelioid fibrosarcoma, with a negative immunohistochemical profile for the expression of MUC4, STAT6, CD34, CK8/18, actin, desmin, S100, and CD45.

Given the nature of the lesion, surgery was performed in June 2019 by *en bloc* resection without residual disease. The study of the piece confirmed the diagnosis of sclerosing epithelioid fibrosarcoma with diffuse expression of MUC4, which supports the diagnosis.

He received adjuvant epirubicin and ifosfamide for three cycles, and radiotherapy to the tumor bed with acceptable tolerance, finishing the treatment in October 2019.

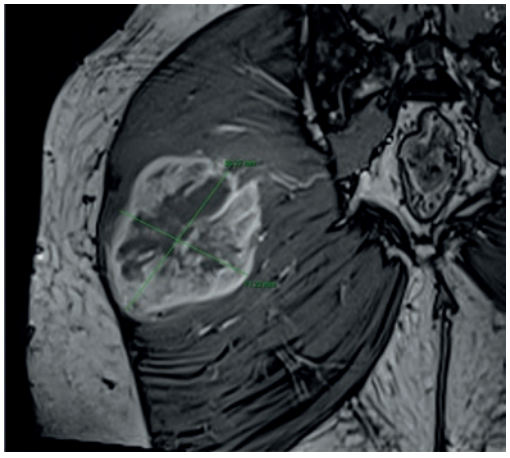

Figure 1. *Primary tumor. Eight cm mass in the right gluteus maximus muscle. The biopsy was positive for sclerosing epithelioid fibrosarcoma.*

In March 2020, he went to the Emergency Unit due to intense neck pain associated with motor deficit, in both upper limbs. An urgent MRI was requested, which visualized a lesion at C5 with a soft-tissue mass occupying the anterior epidural space, associated with stenosis of the spinal canal greater than 50%, and compression of the spinal cord (Fig. 2).

Correspondence:
Fernando Gálvez Montosa
E-mail: fagalmon@gmail.com

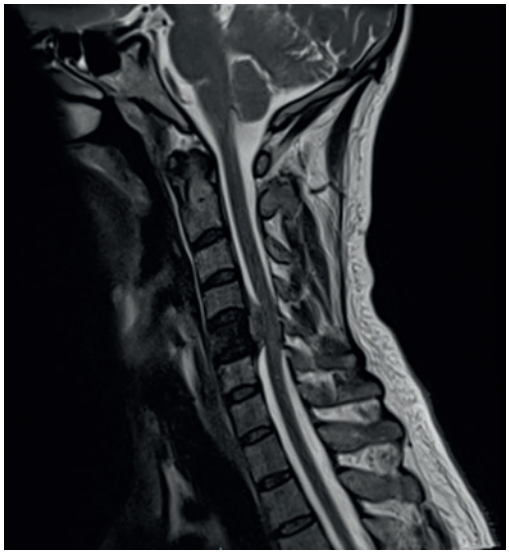

Figure 2. *MRI. Spinal cord compression at C5 level. The vertebral corpse shows diffuse signal alteration due to sarcomatous infiltration.*

He underwent a C5 corpectomy with removal of the epidural mass and anterior cervical cage fixation.

An extension study was requested, in which several pulmonary nodules were observed, the largest being 18 mm. He received adjuvant radiotherapy of 20 Gy with good tolerance, although with slow recovery of mobility due to neck pain, though without sequelae at the motor level.

In June 2020, treatment with gemcitabine-dacarbazine was initiated. After six cycles, pulmonary progression was observed.

Treatment with trabectedin 1.5 mg/m^2 started in January 2021. After 2 cycles with moderate tolerance, dose was reduced to 1.2 mg/m^2 due to grade 2 myalgia and gade 3 hematological toxicity. In reassessment after four cycles, there was a stability of pulmonary lesions.

Treatment with trabectedin was maintained and in successive reassessments, a volumetric reduction of all lung lesions was observed. After 19 months of treatment, the CT shows complete response of some nodules and major partial response in the rest (Figs. 3 and 4). The patient did not present any type of accumulated toxicity and has not required interruptions or further dose delays.

Discussion

Primary sclerosing fibrosarcoma is a very rare and aggressive entity that can be present in adults and the elderly, mainly affecting the lower limbs and, less frequently, the upper limbs, trunk, and head and neck. It is characterized by a high tendency to local relapses and early metastases with an unfavorable prognosis. Histologically, it shows epithelioid

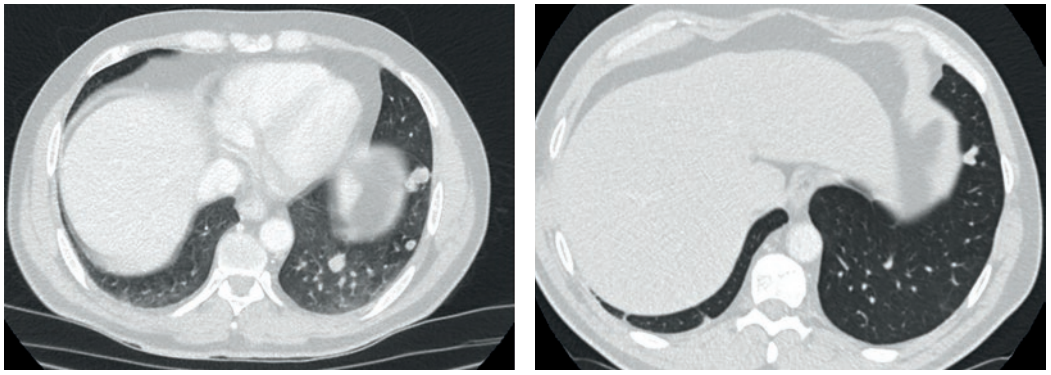

Figure 3. *Left. Lung metastases. Right. Major partial response after 19 months of trabectedin treatment.*

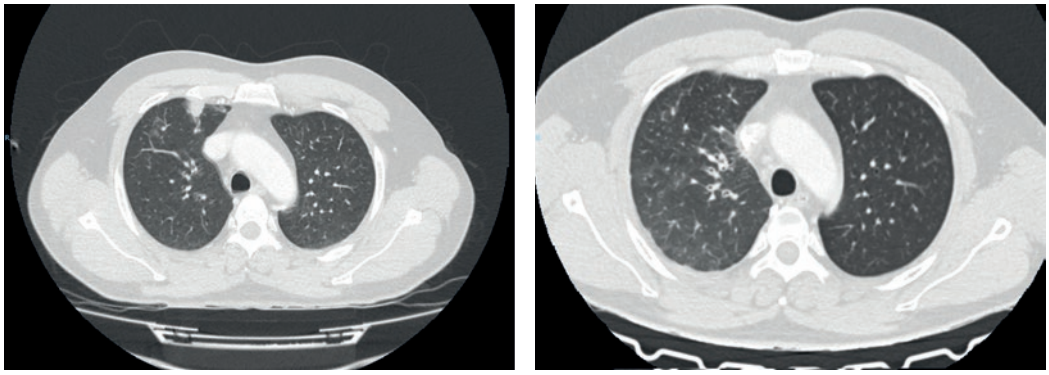

Figure 4. *Complete response of lung metastasis.*

fibroblasts in nests or cords together with a predominantly hyalinized stroma. Elevated immunohistochemical expression of MUC4 appears in 80% of cases[1], which is related to the presence of a fusion protein resulting from the rearrangement between genes EWSR1 and CREB3L1 in most cases, although others have been described[2]. Both manifestations have served to categorize this entity and distinguish it from low-grade fibromyxoid sarcoma, which has a less aggressive clinical course.

Given the extremely rare nature of this tumor, the evidence for a therapeutic algorithm for its management is very limited. The standard treatment, consistent with the rest of soft-tissue sarcomas and by extrapolation, is *en bloc* surgery with wide margins. In this scenario, the role of perioperative treatment is not established, although there are data indicating that radiotherapy treatment can help reduce the local relapse rate, although these are very scarce[3].

At present, the magnitude of the benefit of systemic chemotherapy is not known and the evidence is limited to series of few cases, where most patients were treated with doxorubicin alone or in combination with other classic drugs in the treatment of sarcomas, such as ifosfamide, methotrexate, or cisplatin[4].

Trabectedin is an antitumour agent able to inhibit DNA repair by its bind to the major groove of the double helix and it is reported to inhibit transcription factors derived from fusion proteins, being considered especially effective against translocation-related sarcomas (TRSs).[5] In fact, a pooled analysis of Phase II studies in patients with TRSs showed prolonged disease control and antitumor effects with this agent[5], although, no cases of sclerosing epithelioid fibrosarcoma were included in this study. The evidence on this point comes from isolated cases published in the literature, although with limited benefit[6].

In most responding cases, trabectedin is associated with disease stabilization, which may be linked to changes in density rather than volume, and can sometimes be very long-lasting. However, the response may be delayed in time, so in cases with visceral repercussions, it may be a less appropriate option *a priori*[7].

In our case, the patient currently has a progression-free interval of 19 months since the administration of trabectedin, maintaining a very significant clinical benefit with disease control at all levels and achieving a significant reduction in tumor burden, with a manageable safety profile and maintaining the patient's quality of life and functionality.

To the best of our knowledge, this is the case reported in the literature showing the greatest benefit with trabectedin in this entity.

References

1. Antonescu CR, Rosenblum MK, Pereira P, Nascimento AG, Woodruff JM. Sclerosing epithelioid fibrosarcoma: a study of 16 cases and confirmation of a clinicopathologically distinct tumor. Am J Surg Pathol. 2001;25:699-709.
2. Puls F, Agaimy A, Flucke U, Mentzel T, Sumathi VP, Ploegmakers M, et al. Recurrent fusions between YAP1 and KMT2A in morphologically distinct neoplasms within the spectrum of low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma. Am J Surg Pathol. 2020;44:594-606.
3. Bilsky MH, Schefler AC, Sandberg DI, Dunkel IJ, Rosenblum MK. Sclerosing epithelioid fibrosarcomas involving the neuraxis: report of three cases. Neurosurgery 2000;47:956-9; discussion 959-60.
4. Grunewald TG, von Luettichau I, Weirich G, Wawer A, Behrends U, Prodinger PM, et al. Sclerosing epithelioid fibrosarcoma of the bone: a case report of high resistance to chemotherapy and a survey of the literature. Sarcoma. 2010;2010:431627.
5. Takahashi M, Takahashi S, Araki N, Sugiura H, Ueda T, Yonemoto T, et al. Efficacy of trabectedin in patients with advanced translocation-related sarcomas: pooled analysis of two Phase II studies. Oncologist. 2017;22:979-88.
6. Kobayashi H, Iwata S, Wakamatsu T, Hayakawa K, Yonemoto T, Wasa J, et al. Efficacy and safety of trabectedin for patients with unresectable and relapsed soft-tissue sarcoma in Japan: a Japanese musculoskeletal oncology group study. Cancer. 2020;126:1253-63.
7. Endo M, Takahashi S, Araki N, Sugiura H, Ueda T, Yonemoto T, et al. Time lapse analysis of tumor response in patients with soft tissue sarcoma treated with trabectedin: A pooled analysis of two phase II clinical trials. Cancer Med. 2020 Jun;9:3656-67.