Podcast - Liposarcoma

What is liposarcoma? Key differences by subtype.

Liposarcomas are rare tumours arising from adipose tissue in any part of the body, and they account for approximately 15–20% of all soft tissue sarcomas (STS) (1). Despite their common adipocytic features, liposarcomas are a diverse and heterogeneous group of STS, that can be further classified into distinct histopathological subtypes (2–4):

Atypical lipomatous tumours (ALT) and Well-differentiated liposarcoma (WDLPS) account for 40-45% of all liposarcomas (2). Both entities are low-grade adipocytic tumours often resembling benign lipomas. ALT occur in the extremities, while WDLPS may arise in the retroperitoneum, paratesticular region, mediastinum or head and neck region (5). They represent a locally aggressive neoplasm with virtually no risk of metastatic disease (2,4).

Dedifferentiated liposarcoma (DDLPS) is a high-grade and aggressive disease which arises mostly in the retroperitoneum and deep soft tissue of proximal extremities (6). Up to 90% of cases arise de novo and the remaining 10% develops as a dedifferentiated recurrence of a previous WDL/ATL (6).

Myxoid liposarcoma (MLPS) is the second most common variant, at around 30% of all lipogenic sarcomas. It occurs predominantly in the extremities of young adults and has a disproportionately high metastatic pattern (1,5,7).

Pleomorphic liposarcoma (PLPS) is an aggressive subtype that represents only 5% of all liposarcomas. These tumours most commonly primarily arise in the extremities, followed by the retroperitoneum and the abdomen (5), with distant metastases occurring in up to 50% of cases (2,8).

Finally, the newly described Myxoid pleomorphic liposarcoma (MPLPS), is an exceptionally rare, aggressive, adipocytic neoplasm characterised by a mixture of histologic features from both conventional MLPS and PLPS. It typically occurs in children and adolescents and has a predilection for the mediastinum, with a wide anatomical location (9).

Diagnosis and staging of liposarcoma

The European Society of Medical Oncology (ESMO) guidelines indicate that in primary soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk. Standard radiographs may be useful to rule out a bone tumour whereas computed tomography (CT) has a role in the diagnosis of retroperitoneal liposarcomas. Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple, core needle biopsies (10).

Distinguishing one liposarcoma subtype from another is critical and, in this sense, histologic examination supplemented with molecular studies is essential to obtain accurate diagnosis and plan subsequent treatment strategy, requiring a specialised STS team of pathologists and molecular biologists (4).

For staging purposes, CT scan of the thorax, abdomen and pelvis is recommended in the majority of sarcoma types (10).

Management of localised liposarcoma

All decisions regarding management should be made on an individual basis and by multidisciplinary teams with experience in treating this rare tumour type. The management of localised liposarcoma is determined by tumour size and location. Surgery should be offered as initial management where there is a possibility of complete resection (1).

Preoperative radiotherapy can be discussed in patients with a low-intermediate grade liposarcoma, as signs of efficacy were observed in this subgroup of the Phase III STRASS study (1,10). Regarding preoperative chemotherapy, the STRASS 2 trial will directly assess its role in retroperitoneal sarcoma DDLPS and leiomyosarcoma, but its results are not anticipated until 2028. Meanwhile, it is advisable reserving preoperative chemotherapy for patients with good performance status and borderline resectable or recurrent retroperitoneal sarcomas where tumour shrinkage may improve surgical outcomes (5).

Surgery of local recurrences could be offered especially to WDLPS patients with a long disease-free interval between initial resection and subsequent recurrence, and possibly to patients experiencing a response to medical therapies (10).

Management of advanced liposarcoma

In advanced or metastatic disease, systemic treatments form the mainstay of management and surgery is not usually recommended since it is associated with a poor prognosis irrespective of histological subtype (1). The aim of chemotherapy is to delay and/or relieve tumour-associated symptoms, to improve quality of life and to possibly increase disease specific survival (4).

For over 30 years, **anthracycline-based regimens** have been the recommended **first-line treatment** for advanced liposarcoma (4). A phase III trial concluded that despite improvements in progression-free survival (PFS) and response rate with combination treatment of doxorubicin plus ifosfamide, there was no difference in overall survival (OS) and there was significant additional toxicity compared with single-agent doxorubicin (1). This trial provided a rationale for the continued consideration of **anthracycline monotherapy** for patients who do not require tumour shrinkage for symptom management (5).

Continuous infusion of **high dose ifosfamide** could be a valid option for patients with advanced WDLPS/DDLPS, especially in those patients with a high-grade dedifferentiated component (11). However, in a multicentre phase II study, out of the 13 patients included with liposarcoma, only 1 achieved partial response (PR) and none were complete responders (CR) while experiencing significant toxicity (12).

Gemcitabine and **docetaxel** each have modest activity in sarcomas alone (13). In a recent randomised phase II study, 7 liposarcoma patients were treated with gemcitabine monotherapy. The median PFS was less than 2 months, and the median OS did not reach 6 months (14). In another randomised phase II study that included 20 liposarcoma patients, none of them were responders to gemcitabine alone and 2 achieved PR with the combination (13).

In a randomised phase III trial, OS in previously treated liposarcoma patients was significantly improved with **eribulin** over dacarbazine (15.6 versus 8.4 months), while adverse events were similar between arms (15). Furthermore, eribulin has shown to be favoured in patients who had received ≥ 2 previous regimens, especially if previously treated with trabectedin (16,17).

Trabectedin is the most extensively studied agent to date in advanced liposarcoma, having shown consistent efficacy in more than 400 patients (18).

In a randomised Phase III study comparing trabectedin and **dacarbazine** trabectedin was associated with a 45% reduction in the risk of disease progression or death in 147 patients with advanced liposarcoma. Furthermore, a greater proportion of trabectedin patients (40% vs 16%) received extended treatment courses of 6 or more cycles (19).

Real-life clinical practice studies have also confirmed the efficacy and safety of trabectedin in advanced liposarcoma (20–24). The most recent study is a retrospective analysis in more than 500 STS patients who received trabectedin mainly as second-line treatment (approximately 60%). In the subgroup of 155 liposarcoma patients, a median PFS of almost 9 months and a median OS of 30 months were achieved (20).

The use of trabectedin has also been evaluated in specific liposarcoma histological subtypes. In pre-treated MLPS patients, trabectedin yielded a median PFS of 14 months, a 6-month PFS rate of 88%, an ORR of 51% and a tumour control rate of 90% (25) with consistent results observed in other retrospective studies (23,26). On the other hand, median PFS of almost 4 months have been observed in pre-treated DDLPS (26) and over 13 months in WDLPS patients (27). Clinical case reports in these liposarcoma subtypes and also in PLPS have consistently reported long-term tumour control and quality of life (QoL) preservation (17,24,28–30).

Several other therapies are currently under investigation for the treatment of liposarcomas. CDK4 expression is amplified in approximately 90% of WDLPS/DDLPS cases. A Phase II study of 60 patients treated with palbociclib for WDLPS/DDLPS showed a median PFS of ≈ 4.5 months. Abemaciclib, another CDK4 inhibitor, has already shown promising results in a Phase II study on DDLPS, with a 12-week PFS of 76% (1,5,6). MDM2 amplification is seen in nearly 100% of DDLPS/WDLPS and represents a critical component of tumorigenesis. A phase I study testing the MDM2 inhibitor milademetan in this group of patients reported preliminary clinical activity and an acceptable safety profile and a phase III study is currently ongoing (1,5,6). In terms of immunotherapy, there are ongoing studies targeting the NY-ESO-1 gene with modified T lymphocytes or biclonal antibodies alone or with cytotoxic chemotherapy (1). An ORR of 40% was reported in 10 myxoid/round cell liposarcoma (MRCLS) patients within a phase I study testing an autologous T-cell therapy that targets NY-ESO-1 using a genetically modified, high-affinity T-cell receptor (31). Finally, cabazitaxel, an antimicrotubule agent, has shown promising results in a Phase II trial in DDLPS patients, with 55% of patients being progression-free at 3 months (32).

Conclusions

To conclude, liposarcomas are a diverse and heterogeneous group of STS and an accurate diagnosis is essential to plan an individualised treatment strategy. Surgery should be offered as the initial management of localised liposarcoma whenever there is a possibility of complete resection and, for treatment of advanced disease, anthracyclines are considered the first-line option. Trabectedin is

probably the logical choice for second-line treatment of liposarcoma, since it is able to induce long-lasting tumour control with a preserved QoL, which is the treatment goal for most patients in this setting (33). Additionally, novel therapies targeting a myriad of pathways and known drivers of pathogenesis are actively being explored. A continued understanding and appreciation of the subtype-specific biological underpinnings is essential in optimising treatment approaches and improving outcomes for patients.

References

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Yondelis Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/yondelis#product-information-section

*Yondelis (trabectedin) 0.25mg/ 1mg powder for concentrate for solution for infusion. SmPC Yondelis, July 2021. Yondelis is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

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