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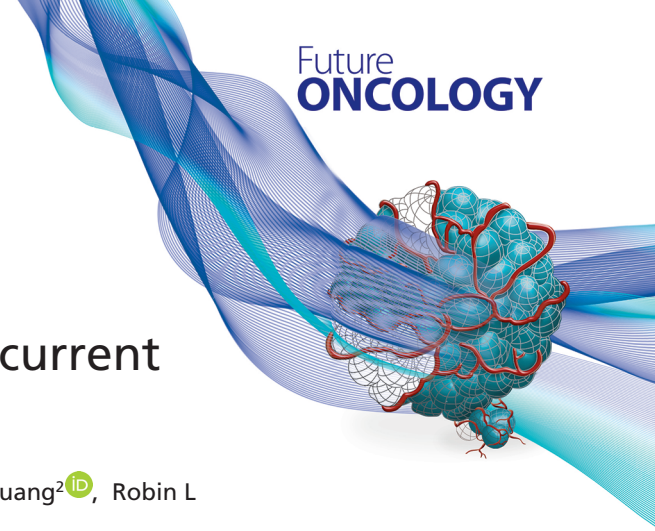

Pharmacotherapy for liposarcoma: current and emerging synthetic treatments

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Liposarcomas are rare tumors arising from adipocytic tissue and accounting for approximately 15–20% of all soft tissue sarcomas. Liposarcoma can be further classified into histopathological subtypes with variable chemosensitivity according to subtype. Decisions regarding management should be made on an individual basis, but surgery for localized disease and systemic chemotherapy remain the mainstay of treatment. Currently, only doxorubicin and trabectedin have robust Phase III data to support their use in the management of advanced liposarcoma. However, in the subgroup analysis of a Phase III trial comparing eribulin with dacarbazine, there was a greater than 7-month improvement in median overall survival in those treated with eribulin. There are also promising results from emerging studies in novel and targeted agents for the treatment of liposarcoma.

First draft submitted: 27 October 2020; Accepted for publication: 18 March 2021; Published online: 21 April 2021

Keywords: liposarcomas • novel therapeutic agents • radiotherapy • systemic chemotherapy • targeted therapies

Sarcomas are a group of rare malignant neoplasms that make up approximately 1% of all adult cancer diagnoses. Liposarcomas, which are mesenchymal malignancies arising from adipose tissues in any part of the body [1], account for approximately 15–20% of all soft tissue sarcomas [2]. The incidence of liposarcoma is approximately 0.6 cases per 100,000 age-adjusted person years based on data from 1978 to 2001 in the USA and 2008 to 2010 in the UK [3,4]. Liposarcoma can be further classified into the following histopathological subtypes: atypical lipomatous tumor/well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma and pleomorphic liposarcoma. In addition, liposarcomas are classified according to grade (high, intermediate and low), which corresponds to the anticipated natural history of the tumor and response to systemic chemotherapy in advanced disease [5,6]. Each subtype has a distinct natural course and clinical behavior, which further complicates treatment options for patients.

WDLPS and DDLPS are the most common tumor subtypes and may demonstrate histopathological features of both subtypes in the same tumor mass. They are therefore considered part of a spectrum of the same histological subtype [1] and account for 50–60% of liposarcomas and 25% of all sarcomas [1,7]. The peak incidence of both subtypes is between 50 and 60 years. WDLPS is found mostly in the extremities and retroperitoneum and is rarely paratesticular or located in the mediastinum [1]. The distribution of DDLPS is similar, but paratesticular, mediastinal and head and neck disease is more common compared with WDLPS [8]. WDLPS and DDLPS are known to arise from the accumulation of chromosomal abnormalities, the most common being 12q13–15 amplification, with *MDM2* being the best described gene in that region [9]. Because of their heterogeneity, the response to chemotherapy is dependent on the proportion of the DDLPS component (which is more chemosensitive than the WDLPS component). Therefore, response rate to chemotherapy in patients with DDLPS/WDLPS is approximately 11–24%. For patients with unresectable, localized disease, systemic therapy is not usually recommended unless the patient is symptomatic or has complications resulting from their disease [5,7,10]. A 2017 single-center retrospective study reviewed outcomes and treatment efficacy in 82 patients with DDLPS and WDLPS of the retroperitoneum treated with first-line chemotherapy (including 51 patients with advanced disease) and found that patients typically

received combination chemotherapy (88%) with an anthracycline agent (80%) [10]. Partial response was seen in 20% of patients (10 of 51), with stable disease seen in 33% (17 of 51), and 47% of patients progressed on treatment (24 of 51). In this group of patients, median progression-free survival (PFS) was 4 months, with median overall survival (OS) of 25 months.

Myxoid/round cell liposarcoma accounts for approximately 30–40% of all liposarcomas and approximately 5% of all sarcomas [1]. The peak incidence of this subtype usually occurs between 30 and 50 years, although it can occur in childhood and adolescence. The most common sites are the thighs and other proximal extremities. Like WDLPS/DDLPS, these tumors may also be considered part of a spectrum of the same histological subtype. A total of 90–95% of tumors express the *FUS-DDIT3* gene, with most of the remaining tumors expressing the related *EWSR1-DDIT3* gene [11]. These tumors are typically more chemosensitive and radiosensitive compared with other liposarcoma subtypes [5]. A study of perioperative radiotherapy in patients with extremity myxoid liposarcoma found a 5-year local recurrence-free survival of 97.7% and metastasis-free survival of 93.9% [12].

Pleomorphic liposarcoma is the rarest subtype, representing approximately 5–10% of all liposarcomas. The molecular pathology underpinning this subtype is poorly understood, with likely complex karyotypes characterized by multiple chromosomal gains and losses, including loss of *RB1* (13q14.2–5) and mutations or loss of *TP53* [13,14]. The peak incidence of pleomorphic liposarcoma is over 50 years of age, and the disease is most commonly found in the upper and lower limbs [8]. This subtype is high-grade, clinically aggressive and associated with poor clinical outcomes and high rates of local recurrence and distant metastasis [1]. There is a paucity of evidence to guide systemic chemotherapy treatment in this histological subtype [5]. However, it is known that these tumors are not particularly chemosensitive, and a retrospective study of 32 patients demonstrated an overall response rate to systemic chemotherapy treatment of 37% [15].

All decisions regarding management should be made on an individual basis, taking into consideration tumor size, histopathological subtype, site of disease and patient factors, by multidisciplinary teams with experience in treating this rare tumor type [16,17]. Management of localized liposarcoma is determined by tumor size and location. Where there is a possibility of complete resection, surgery should be offered as initial management. In retroperitoneal sarcomas, the Phase III STRASS study did not demonstrate benefit of preoperative radiotherapy for reducing relapse-free survival. However, in the *post-hoc* second sensitivity analysis (where patients who had progressed or had become medically unfit during their planned radiotherapy were included provided they had a macroscopically complete surgical resection), there was a suggestion of benefit in 3-year abdominal relapse-free survival in the liposarcoma cohort with preoperative radiotherapy compared with surgery alone (75.7 vs 65.2%; hazard ratio [HR]: 0.62; 95% CI: 0.38–1.02). In the abdominal recurrence-free survival subgroup analysis, there was also a suggestion that the WDLPS subgroup could benefit from preoperative radiotherapy (HR: 0.69; 95% CI: 0.33–1.46), but further studies are warranted [18]. Despite surgical resection with clear margins, the risk of developing relapsed disease remains high; however, outcomes are improved when treatment is delivered at specialist centers with experience in managing this rare disease [19]. In a single-center retrospective study of patients with retroperitoneal liposarcoma treated with surgery with curative intent, disease-specific survival was only 73% at 3 years and 60% at 5 years [17,20]. In advanced or metastatic disease, systemic treatments, with or without locoregional treatments, form the mainstay of management. Surgery may occasionally be offered in advanced or oligometastatic disease at the discretion of the multidisciplinary team but is not usually recommended since it is associated with a poor prognosis irrespective of histological subtype [16,17].

Currently available systemic therapies in liposarcoma

Doxorubicin

Anthracycline-based treatment, typically with doxorubicin, continues to remain first-line treatment since several Phase III trials have not demonstrated benefits in OS with combination treatment. The multicenter, open-label, Phase III European Organisation for Research and Treatment of Cancer (EORTC) 62012 study concluded that despite improvements in PFS and response rate with combination treatment, there was no difference in OS and significant additional toxicity with combination doxorubicin plus ifosfamide compared with single-agent doxorubicin [21]. A subgroup analysis of this study highlighted the importance of a central pathology review in such studies, with a 32% discordance in tumor histology and 39% discordance in tumor grade. Also, patients with liposarcoma, without subtype information, responded better to chemotherapy compared with patients in all other

histological subgroups (p = 0.14) [22]. Additionally, a single-center retrospective review of high-dose ifosfamide in 11 patients with myxoid liposarcoma deemed it to be inactive, with a median PFS of 1.9 months [23].

High-dose ifosfamide

There are limited data on the use of single-agent ifosfamide in liposarcoma. A retrospective study of 28 patients with WDLPS and WDLPS/DDLPS treated with high-dose ifosfamide (14-day continuous infusion of 14 g/m^2 every 28 days) suggested the treatment was very effective, and six of the nine patients who had minor or partial response had previously had only stable disease with combination doxorubicin/ifosfamide. This therapy was, however, very toxic, with seven of 20 nonprogressing patients discontinuing treatment because of toxicity [24].

Trabectedin

Trabectedin is a marine-derived drug with a complex mechanism of action that is not fully understood. In the European Union, it is currently offered in the advanced or metastatic setting after failure of anthracycline treatment in patients with liposarcomas and leiomyosarcomas as well as other soft tissue sarcomas. A retrospective study of 51 patients with pretreated myxoid liposarcoma demonstrated an overall response rate of 51%, with a complete response in two patients [25] The interim results of a Phase III, randomized, multicenter study comparing trabectedin with dacarbazine in 518 patients, including 140 with liposarcomas, were published in 2016 [26]. In the liposarcoma arm, there was an increase in median PFS in the trabectedin group compared with the dacarbazine group (5.6 vs 1.5 months, respectively) as well as improvements in 3- and 6-month progression-free rates in the trabectedin group (56 and 37%, respectively). In the subgroup analysis, trabectedin showed greatest efficacy in improving PFS in the myxoid subtype of liposarcoma. A randomized Phase II study also showed that there was a statistically improved PFS in patients with sarcoma, including liposarcomas, who continued with trabectedin beyond six cycles of treatment [27]. This was not linked to increased toxicity but did not translate to a statistically significant prolongation of OS. Therefore, the duration of trabectedin treatment in patients with stable disease remains to be defined. Although systemic chemotherapy is not routinely offered to patients with localized liposarcoma, a Phase II trial of neoadjuvant trabectedin with locally advanced myxoid liposarcoma was performed with pathological complete response or tumor regression rate as the primary end point [28]. A total of 13% of patients (3 of 23) had a pathological complete response, with moderate response in 52% of patients (12 of 23) and partial response in 24% (7 of 23), with no patients progressing while on treatment and toxicity profiles in keeping with the existing literature for trabectedin. In another international, open-label, randomized, controlled, Phase III, multicenter, neoadjuvant trial (Italian Sarcoma Group–Soft Tissue Sarcoma 1001), patients with high-grade myxoid liposarcoma were randomized between three-weekly epirubicin 60 mg/m^2 per day (days 1 and 2) plus ifosfamide 3 g/m^2 per day (days 1–3) and trabectedin (1.3 mg/m^2) [29]. Disease-free survival was similar in the two groups (HR: 1.03; 95% CI: 0.24–4.39), providing further evidence of the efficacy of trabectedin in this setting.

Eribulin

Eribulin is currently licensed for use in patients with liposarcomas that have progressed following treatment with an anthracycline. Eribulin acts by disrupting microtubule polymerization by sequestering tubulin dimers to aggregate into globular structures. These cannot be utilized by the cell, leading to cell growth arrest and apoptosis. Eribulin also works by reversing epithelial-to-mesenchymal transition [30]. In the subgroup analysis of the liposarcoma cohort of the Phase III eribulin versus dacarbazine trial, median OS improved by 7.2 months with eribulin ($p < 0.001$), with improved PFS (2.9 vs 1.7 months; p = 0.0015), without additional toxicity [31,32]. The OS difference was statistically significant only for patients with advanced/metastatic DDLPS and pleomorphic liposarcoma and did not reach significance for myxoid/round cell liposarcoma. Specifically, in patients with pleomorphic liposarcoma, who represented only 16.1% of all patients included in the study, the OS difference was 22.2 in the eribulin arm versus 6.7 months in the dacarbazine arm [32]. The preliminary results of the Phase I/II LEADER study, which compared the efficacy of combination lenvatinib and eribulin in soft tissue sarcomas (including six patients with liposarcomas), were recently presented ahead of publication [33]. Median PFS was 12.9 months, and the 6-month PFS rate was 72%, with no unexpected toxicities.

Gemcitabine

Single-agent gemcitabine has modest activity in soft tissue sarcomas, including liposarcomas [34,35], but in combination with docetaxel leads to an improvement in objective response rate (16 vs 8%), median PFS (6.2 vs 3.0 months)

Table 1. Summary of results of Phase II, III and postmarketing studies that have demonstrated efficacy in liposarcoma.

Treatment class	Drug	Mechanism of action	Relevant study	Participants, n	Efficacy in liposarcoma	Ref.
TKI	Pazopanib	Antiangiogenic Antitumorogenic	Phase II	17	Liposarcoma arm closed to recruitment early because of failure to meet primary end point in stage I; however, in final analysis, two patients were reclassified, which would have allowed the liposarcoma cohort to proceed to full enrollment in stage II	[41]
			Phase II	52	Median PFS 3.5 months, median OS 16.4 months in WDLPS/DDLPS cohort, but myxoid cohort closed to recruitment early	[43]
			Phase II	41	A total of 74.1% of patients (20 of 27) with DDLPS and 66.7% of patients (8 of 12) with myxoid liposarcoma met the primary end point of PFR at 12 weeks	[42]
			Phase III	–	Liposarcoma excluded based on EORTC 62043	[40]
			Retrospective study	32	Does not support the use of pazopanib in liposarcoma	[45]
	Regorafenib	Antiangiogenic Antistromal Antitumorigenic	Phase II	182	Did not meet primary end point of improved PFS compared with placebo	[49]
	Anlotinib	Antiangiogenic	Phase II	233	For liposarcoma, PFS at 12 weeks was met in 63% of patients, median PFS was 5.6 months and OS was 13 months	[50]
	Sunitinib	Antiangiogenic	Phase II	48	PFS was 3.9 months and OS 10.1 months in the liposarcoma arm of the trial	[51]
CDK inhibitor	Palbociclib	CDK4 and CDK6 inhibitor	Phase II	60	Efficacy in DDLPS/WDLPS; CR in one patient; median PFS was 17.9 weeks, with a PFR at 12 weeks of 57.2%	[56]
Nuclear export inhibitor	Selinexor	Inhibits *XPO1*	Phase II/III	56	Median PFS 5.6 months in DDLPS; study currently recruiting for Phase III stage	[70]
Thiazolidinedione	Troglitazone	PPARγ receptor agonist	Phase II	3	Histological evidence of activity, with increased differentiation of tumor on post-treatment biopsy	[72]
AURKA inhibitor	Alisertib	Inhibits the AURKA protein	Phase II	72	Did not meet the primary end point for response rate in liposarcoma; however, the secondary end point of 12-week PFS was met in 73% of patients with liposarcoma	[84]

CR: Complete response; DDLPS: Dedifferentiated liposarcoma; EORTC: European Organisation for Research and Treatment of Cancer; OS: Overall survival; PFR: Progression-free rate; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; WDLPS: Well-differentiated liposarcoma.

and median OS (17.9 vs 11.5 months), although with increased toxicity compared with gemcitabine alone [36]. A randomized, placebo-controlled, Phase II trial provides a benchmark for the efficacy of the combination of gemcitabine and docetaxel in liposarcomas, with a median PFS of 5.6 months (95% CI: 2.6–8.3 months) in the gemcitabine/docetaxel/placebo arm versus 4.3 months (95% CI: 2.7–6.3 months) in the gemcitabine/docetaxel plus ontuxizumab (monoclonal antibody to endosialin) arm [37].

Dacarbazine

Dacarbazine has minimal activity in liposarcoma but historically has been used in the second line for treatment of advanced liposarcoma. However, modest improvements in OS are seen when dacarbazine is used in combination with gemcitabine [38].

Emerging systemic therapies in liposarcoma

There are several emerging systemic therapies that are currently under investigation in liposarcoma, and these are summarized in Table 1.

Tyrosine kinase inhibitors

Pazopanib is an oral tyrosine kinase inhibitor used in the treatment of other solid tumors, including soft tissue sarcomas [39,40]. Pazopanib has antiangiogenic and antitumorigenic properties mediated by the semiselective inhibition of several growth factor receptors (VEGFR, PDGFR, FGFR and c-KIT) found inside many solid tumors. Because of the exclusion of the liposarcoma subtype from the Phase III PALETTE study after provisional data from the EORTC 62043 study demonstrated lack of efficacy, the role of pazopanib in liposarcomas remains unclear [40,41]. However, in the final analysis, two patients in the EORTC 62043 study were reclassified as having liposarcoma, and

had they been included in the provisional analysis, liposarcoma would have met the predefined study requirement that pazopanib should achieve a progression-free rate of >20% at 12 weeks, warranting a further Phase III study [41].

Several other Phase II studies have shown promising activity of pazopanib in liposarcoma, but results among the different histopathological subtypes are somewhat conflicting, although one Phase II multicenter study demonstrated efficacy in the DDLPS and myxoid liposarcoma subtypes [42]. A German and Spanish collaborative Phase II trial closed their myxoid cohort to recruitment early because of failure to meet the primary end point [43]. However, in the WDLPS/DDLPS subgroup of this same study, 43.2% of patients met the primary end point. The provisional results of the Phase II randomized EPAZ trial in elderly patients demonstrated noninferiority of pazopanib to doxorubicin in liposarcoma [44]. However, in a retrospective multicenter postmarketing study performed in Japan, pazopanib performed poorly in liposarcoma, with a median PFS of 8 weeks compared with other sarcoma subtypes [45]. Despite the paucity of Phase III evidence to support the use of pazopanib in liposarcoma, the role of combination pazopanib and other systemic therapies is currently being explored further with both topotecan [46] and gemcitabine [47].

Regorafenib is another oral tyrosine kinase inhibitor with antiangiogenic, antistromal and antitumorigenic properties and is currently either in use or under investigation in metastatic colorectal cancer, renal cell carcinoma, hepatocellular carcinoma and gastrointestinal stromal tumor [48]. However, regorafenib did not meet the primary end point of improved PFS (as per Response Evaluation Criteria in Solid Tumors 1.1) compared with placebo in the liposarcoma cohort of the REGOSARC trial in patients pretreated with an anthracycline [49]. In this study, conducted on patients with liposarcoma, PFS for those treated with regorafenib was 1.1 months compared with 1.7 months in the placebo arm.

Other tyrosine kinase inhibitors that have been under investigation for use in liposarcoma include anlotinib [50], sunitinib [51], sitravatinib [52], nintedanib [53] and axitinib [54]. In the recently presented results of a Phase II trial, anlotinib showed activity in soft tissue sarcomas [50]. In the liposarcoma subgroup of this study, PFS at 12 weeks was observed in 63% of patients (n = 13), with median PFS of 5.6 months and OS of 13 months. A Phase II study of patients with soft tissue sarcomas treated with sunitinib also demonstrated promising results [51]. In the liposarcoma arm of the trial, PFS was 3.9 months and OS was 10.1 months. However, results of outcomes for patients with liposarcoma treated with sitravatinib [52], nintedanib [53] and axitinib [54] in their respective Phase II trials are awaited.

CDK inhibitors

Palbociclib is an oral CDK inhibitor treatment that is currently licensed for use in the treatment of breast cancer [55]. *CDK4* expression is amplified in approximately 90% of cases of WDLPS/DDLPS, and palbociclib can induce tumor senescence by selectively inhibiting the *CDK4* and *CDK6* expressed by the tumor. The results of a Phase II single-center study of 60 patients treated with palbociclib for WDLPS/DDLPS were published in 2016 [56]. The results were promising, with complete response in one patient. Median PFS was 17.9 weeks, with a progression-free rate at 12 weeks of 57.2% and a manageable toxicity profile. The Phase II PalboSarc study of palbociclib is currently recruiting patients with other soft tissue sarcomas that overexpress *CDK4* [57]. There are two other CDK inhibitors currently under investigation in liposarcoma: ribociclib [58] and abemaciclib [59]. Abemaciclib, a potent CDK4 inhibitor, has already shown promising results in a Phase II study on DDLPS, with a 12-week PFS of 76% (95% CI: 57–90%). However, dose-limiting myelosuppression (particularly neutropenia), diarrhea, nausea, vomiting and fatigue are seen frequently with this therapy [56,60]. Unfortunately, resistance to CDK inhibitor therapy may develop, and there is an unmet need for suitable combination agents to help combat this resistance.

MDM2 inhibitors

In addition to CDK overexpression, amplification of the *MDM2* gene contributes to tumor growth in WDLPS. The MDM2 inhibitor milademetan (DS-3032b) has shown promising results in solid tumors, including DDLPS. Although the development of milademetan has taken some time, with extensive evaluation in the Phase I setting, a Phase III study is currently in startup [61,62]. The combination of another MDM2 inhibitor (RG7388) with palbociclib has a synergistic effect, and an early-Phase study has demonstrated decreased tumor growth rate and increased PFS [63]. This may also open the possibility of a novel combination therapeutic option with M2M2 inhibitors and CDK inhibitors in the future.

mTOR inhibitors

The mTOR inhibitors are currently under investigation for treatment of liposarcoma, including sirolimus and cyclophosphamide in myxoid liposarcoma [64] and ribociclib and everolimus in DDLPS [65]. The Phase III, randomized, placebo-controlled SUCCEED study included 99 patients with liposarcoma treated with ridaforolimus [66]. Overall, the study demonstrated a 12% increase in clinical benefit rate of ridaforolimus compared with placebo ($p < 0.001$), with a significant increase in median PFS (17.7 vs 14.6 weeks) compared with placebo ($p < 0.001$), but unfortunately the researchers did not publish the results of subgroup analysis for the histological subtypes.

Selinexor

Selinexor is a novel nuclear export inhibitor that targets *XPO1*. Overexpression of *XPO1* is associated with increased cell survival due to nuclear accumulation of proteins that inhibit tumor suppressor genes. Overexpression of *XPO1* has been found in several tumor types [67]. Results from a Phase I study of selinexor in 54 patients with soft tissue sarcomas were published in 2016 [68]. In this study, despite no patients having an objective response (as per Response Evaluation Criteria in Solid Tumors 1.1), it was noted that in the cohort of patients with DDLPS, 40% (six of 15) had a reduction in the size of their target lesion and 47% (7 of 15) had a durable period (≥4 months) with stable disease. In addition, analysis of the 16 patients with evaluable paired biopsies demonstrated a reduction in cellularity and proliferation and an increase in apoptosis and fibrosis following treatment with selinexor. The Phase II/III placebo-controlled SEAL study of selinexor in patients with DDLPS showed promising improvements in median PFS in the Phase II study [69], and results from the Phase III study were presented ahead of publication in 2020 [70]. Median PFS was 2.83 months in the selinexor arm versus 2.07 months in the placebo arm (HR: 0.70; $p = 0.023$).

Thiazolidinediones

PPARγ is a regulator of adipocyte differentiation. Thiazolidinedione drugs (which are licensed for use in diabetes mellitus and include rosiglitazone, troglitazone and efatutazone) act as agonists of PPARγ receptors and thus have potential anticancer activity. Despite failing to demonstrate efficacy of rosiglitazone in a Phase II study of liposarcoma patients [71], an earlier Phase II study of three patients treated with troglitazone demonstrated promising results, with histological evidence of activity, with increased differentiation of the tumor on post-treatment biopsy [72]. Efatutazone has been shown to have efficacy in advanced solid organ tumors in a Phase I study [73] and is currently under investigation in patients with advanced myxoid liposarcoma [74].

Cabazitaxel

Cabazitaxel is an antimicrotubule agent (in the same class as eribulin [32]) that targets the protein tubulin, which is required for cell division and growth. It is currently licensed in prostate cancer [75] and has demonstrated safety, efficacy and tolerability in Phase I trials of solid organ tumors [76]. Cabazitaxel is currently under investigation in a Phase II trial for liposarcoma that is now closed to recruitment [77].

Immunotherapies

The efficacy of immunotherapy in soft tissue sarcomas is currently poorly understood. The results of a Phase II study of pembrolizumab demonstrated some activity in the dedifferentiated liposarcoma subgroup but did not meet the primary end point in the expansion subgroup [78]. A Phase II study of neoadjuvant radiotherapy with neoadjuvant nivolumab or combination nivolumab plus ipilimumab in patients with resectable dedifferentiated liposarcoma of the retroperitoneum is currently recruiting [79].

Other ongoing studies are targeting the *NY-ESO-1* gene with modified T lymphocytes or biclonal antibodies alone or with cytotoxic chemotherapy. The aim of these treatments is to attack the target tissue mainly via cytotoxic T lymphocyte killing as well as with accessory immune mechanisms. A prerequisite for participation in these studies is tumor expression of *NY-ESO-1* in the study prescreening [80,81]. In a study with 12 patients with synovial sarcoma, overall response rate was 50%, with one complete response [82]. Median duration of response was 30.9 weeks, and there were no significant complications. Myxoid liposarcomas also express high levels of NY-ESO-1 antigen; thus, it is therefore considered an excellent candidate for further studies with adaptive T-cell therapy [83].

Alisertib

AURKA is a protein commonly overexpressed in soft tissue sarcomas and is responsible for cancer cell proliferation. Alisertib is an AURKA inhibitor that has been shown to block this proliferation in early-phase studies. A Phase II study did not meet the primary end point for response rate in liposarcoma; however, the secondary end point of 12-week PFS was met in 73% of patients with liposarcoma, with manageable toxicity profile [84].

Neoadjuvant chemotherapy with regional hyperthermia

The EORTC 62961-ESHO 95 Phase III randomized trial looked into the effects of neoadjuvant chemotherapy combined with regional hyperthermia in the treatment of localized, high-risk soft tissue sarcomas [8]. This study showed that neoadjuvant chemotherapy combined with regional hyperthermia led to a 27% improvement in survival and a statistically significant improvement of 11.4 and 9.9% in 5- and 10-year survival rates, respectively, compared with neoadjuvant chemotherapy alone. Improved survival was specifically observed in 'L-sarcomas' (leiomyosarcoma and liposarcoma) and in all other high-grade histological subtypes.

There is thus far no evidence that nanodrugs are effective against liposarcoma. Nanoparticles have been used in combination with hyperthermia, but the limited evidence so far suggests that this is not an effective strategy [85].

Discussion & conclusion

Like many other sarcoma subtypes, there remains a paucity of treatment options for locally advanced or metastatic liposarcoma. Currently, only doxorubicin [21], trabectedin [26] and eribulin [31] have Phase III data to support their efficacy in advanced soft tissue sarcomas, including liposarcoma. Several emerging systemic therapeutic agents from a range of different classes have shown promise in Phase II clinical trials to date, including tyrosine kinase inhibitors [42-44], CDK inhibitors [56], mTOR inhibitors [86], thiazolidinediones [72] and selinexor [69]. Several other agents from the same classes as these agents as well as cabazitaxel [77] and immunotherapy agents are currently under investigation in Phase II clinical trials [79]. Further work in Phase III randomized clinical trials is required to explore the efficacy of these newer treatments in the management of liposarcomas, including further biomarker-led studies to investigate additional targets for treatment.

There remains an unmet need for effective treatments for advanced and metastatic liposarcoma. There are a wide range of systemic treatments from a variety of different classes that have shown promise in early-phase clinical trials and are currently being investigated in Phase III studies for use in the treatment of advanced or metastatic liposarcoma, including pazopanib [42-44], anlotinib [50], sunitinib [51], palbociclib [56], troglitazone [72] and selinexor [69]. This has the potential to increase the number of treatment options for patients with liposarcoma. Many of these treatments have significant advantages over existing treatments [21,26] for liposarcoma, including their oral route of administration and comparatively reduced hematological toxicity. However, randomized Phase III trials and head-to-head data to support their use are currently lacking, and this is currently preventing adoption of these emerging treatments in clinical practice.

The current focus for liposarcoma is developing or repurposing treatments that target proteins involved in cancer pathways. Many of the treatments currently under investigation have biomarker-targeted activity, including palbociclib [56] and selinexor [69]. We also anticipate that there will be a greater utilization of combination therapy with systemic chemotherapy and oral targeted agents, depending on the outcomes of several studies that are currently underway [47,87].

Future perspective

Further work to understand the pathways influenced by genes expressed by the different subtypes of liposarcoma may be helpful in building a greater understanding of the pathogenesis of these subtypes and developing effective therapeutic agents. We expect that in the future most patients with liposarcoma will be treated using a more focused histology-led approach to treatment while moving away from the conventional chemotherapy options. We also expect that there will be a wider range of treatments available to patients with this disease.

Executive summary

Background

- There remains an unmet need for effective treatments for advanced and metastatic liposarcomas.

Currently available systemic therapies in liposarcoma

- There are several currently available therapies for liposarcoma, which include doxorubicin, high-dose ifosfamide, trabectedin, eribulin, gemcitabine and dacarbazine.

Emerging systemic therapies in liposarcoma

- There are several emerging systemic therapies that are currently under investigation in liposarcoma, including tyrosine kinase inhibitors, CDK inhibitors, MDM2 inhibitors, mTOR inhibitors, selinexor, thiazolidinediones, cabazitaxel, immunotherapies and alisertib.
- Other emerging treatments include neoadjuvant chemotherapy with regional hyperthermia.

Discussion & conclusion

- There are a wide range of systemic treatments that have shown promise in early clinical studies for use in the treatment of advanced or metastatic liposarcoma.
- Data to support newer agents are currently lacking, and this is currently preventing adoption of these emerging treatments in clinical practice.

Financial & competing interests disclosure

RL Jones is the recipient of grants/research support from MSD and GlaxoSmithKline and receives consulting fees from Adaptimmune, Athenex, Blueprint, Clinigen, Eisai, Epizyme, Daiichi Sankyo, Deciphera, Immune Design, Lilly Merck, Pharmamar and UptoDate. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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