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REVIEW

Maintenance therapy and drug holiday in sarcoma patients: systematic review

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ABSTRACT

Purpose: Overall prognosis of advanced sarcoma remains poor, optimization of systemic treatment is urgently needed in this setting.

Materials and methods: We systematically reviewed fully published English-speaking literature about maintenance therapy and drug holiday in sarcoma patients management.

Results: We found that switch maintenance therapy with cyclophosphamide/vinorelbine improves the outcome of localized high-risk rhabdomyosarcoma. There is no other maintenance therapy recommended in sarcoma patients. After classical chemotherapy, maintenance therapy with immune-stimulating agents for localized osteosarcoma, bevacizumab for advanced angiosarcoma or pediatric advanced sarcoma, or mTOR inhibitors for metastatic sarcoma does not improve the outcome. Drug holiday has been assessed for metastatic gastrointestinal stromal tumor treated with imatinib as the first-line therapy or for metastatic soft-tissue sarcoma treated with trabectedin. Drug holiday has been found to lead to rapid disease progression and should be avoided.

Conclusions: Data about both maintenance and drug holiday are spare in sarcoma management.

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Abbreviations: 95% CI: 95% confidence interval; CTX: cyclophosphamide; DFS: disease-free survival; EFS: event-free survival; GIST: gastrointestinal stromal tumor; IFNα: interferon-alpha; ITT: intention to treat (analysis); IVA: ifosfamide/vincristine/actinomycin; IVADo: ifosfamide/vincristine/actinomycin/doxorubicin; MAI: methotrexate/doxorubicin/ifosfamide; MAP: methotrexate/doxorubicin/cisplatin; mTOR: mammalian target of rapamycin; MTP: muramyl tripeptide phosphatidylethanolamine; OS: overall survival; n: number of patients; p: p-value; PFS: progression-free survival; PP: per protocol (analysis); RIDA: ridaforolimus; RMS: rhabdomyosarcoma; VIN: vinorelbine

Introduction

Sarcomas include a large number of clinico-pathological entities with variable aggressiveness. Management of some localized sarcomas could require adjuvant or neoadjuvant treatments. Most patients with metastatic/advanced disease are best treated with systemic and palliative therapies that primarily aim to alleviate symptoms and improve quality of life. The toxicity/efficacy ratio of systemic treatments needs to be cautiously weighted.

Maintenance therapy gathers different approaches depending on both the clinical setting (curative-intent versus palliative treatment) and the nature of maintenance therapy (continuation maintenance therapy versus switch maintenance).

Traditionally, at advanced stage, not amenable to curative-intent strategy, systemic treatment could be administered until severe toxicity, disease progression, or cumulative dose have been reached (e.g., as in the case of doxorubicin). After the administration of classical chemotherapy and in the absence of disease progression (including complete or partial response or stable disease), maintenance therapy could be discussed. Maintenance therapy aims to maintain response, prevent or delay progressive disease, and improve quality of life. In this setting, there is no consensus on maintenance therapy duration. In this setting, the key-difference between maintenance therapy and further line is that maintenance therapy is given in patients experiencing non-progressive disease and further line is given in those experiencing progressive disease.

At the localized stage, maintenance therapy could be used to maintain complete response and delay or reduce the risk of relapse. Maintenance therapy is then part of (neo)adjuvant strategies. In contrast, at the metastatic/advanced stage, drug holiday, which is planned discontinuation of systemic treatment providing stable disease or response, is considered with the aim to reduce treatment-related toxicity and improve the quality of life. Usually in this setting the duration of maintenance therapy is clearly defined.

At least two different kinds of maintenance therapy have been established: (i) same regimen at a lower dose or a part of the 'induction' treatment ('continuation maintenance therapy'), or (ii) use of another drug after administration of 'induction' treatment ('switch maintenance therapy').

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Supplemental data for this article can be accessed here.

In the present review, we summarize available fully English-written published trials assessing maintenance therapy and drug holiday in sarcoma patients. This systematic review was conducted using Medline Database (last searched on 24 November 2019) and according to PRISMA guidelines [1]. Only English-written prospective clinical trials assessing 'drug-holiday' or 'maintenance therapy' in 'sarcoma' patients have been retained. The following filters ('trials' and 'humans') and terms have been used for searching articles 'treatment interruption + Sarcoma' (30 articles), 'maintenance therapy + Sarcoma' (58 articles). Articles have been selected after abstract reading. All articles have been checked by all authors. Additional references have been added after reading of the selected articles.

Results

Maintenance therapy in curative-intent settings

Use of immune-stimulating agents in osteosarcoma patients

Osteosarcoma is treated by preoperative chemotherapy, followed by curative-intent surgery and then adjuvant chemotherapy. Adjuvant chemotherapy could be adapted according to the rate of chemotherapy-induced tumor necrosis. Surgery is the best treatment in cases of limited relapse (e.g., limited lung metastasis). In the case of diffuse metastasis, there is no consensus on treatment and no recognized active salvage treatment. Therefore, the efficacy of (neo)adjuvant chemotherapy is critical for improving outcomes, and the addition of maintenance therapy is an appealing approach in this context. Two immune-stimulating agents have been assessed as maintenance therapy in patients with localized high-grade osteosarcoma receiving adjuvant chemotherapy in two large phase 3 trials (Table 1).

The rationale for using interferon-alpha (IFNα) as maintenance therapy is based on (i) the fact that IFNα acts as an antiproliferative, differentiation-inducing, pro-apoptotic, and antiangiogenic agent and (ii) the fact that some osteosarcomas could express IFN receptors [2,3]. Müller et al. reported their experience of 89 localized high-grade osteosarcomas treated between 1971 and 1990 with IFNα without chemotherapy. With a median follow-up period of 12 years, the observed 10-year metastasis-free and sarcoma-specific survival rates were 39% and 43%, respectively. The data of this retrospective series were regarded as promising [2]. Therefore, the EURAMOS group launched a large phase 3 trial assessing the role of IFNα after (neo)-adjuvant therapy for localized high-grade osteosarcoma ($n = 716$) [3]. The patients received two cycles of methotrexate/doxorubicin/cisplatin as preoperative treatment and then underwent curative-intent surgery. Good responders were randomly assigned to receive four additional cycles of chemotherapy or four additional cycles of chemotherapy followed by weekly subcutaneous IFNα-2b for 74 weeks. The primary objective of the trial was to improve event-free survival (EFS) (Table 1). Approximately 18% (64/357) of the patients assigned to the experimental arm refused IFNα-2b. IFNα-2b was prematurely stopped due to toxicity in approximately 13% of the patients assigned to the experimental arm. Of the 271 patients actually treated with IFNα-2b, 132 (49%) required dose reduction or delays. There was no improvement in both the 3-year EFS and overall survival (OS) (Table 1).

Muramyl tripeptide phosphatidylethanolamine (MTP), a nonspecific immune modulator, is a synthetic analog of a bacterial membrane. Studies with preclinical models suggest that MTP has antitumoral effects. An exploratory phase II trial was conducted in 16 patients with metastatic osteosarcoma; pharmacodynamic endpoints were reported but clinical endpoints were not reported in this trial [4]. Meyers et al. reported a large phase 3 trial with a factorial design. The patients in this trial were first randomly assigned to receive two cycles of preoperative chemotherapy with methotrexate/doxorubicin/cisplatin (MAP) *versus* two cycles of methotrexate/doxorubicin/ifosfamide (MAI) [5,6]. The patients underwent curative-intent surgery. After surgery, the patients were divided into four arms: MAP (as an adjuvant regimen) *versus* MAP + MTP followed by MTP alone *versus* MAI *versus* MAI + MTP followed by MTP alone. MTP was administered twice weekly for 12 weeks beginning at week 12 and weekly for an additional 24 weeks beginning at week 24. Using the factorial design, the authors determined that 585 patients were needed to observe an EFS improvement with an expected hazard ratio of 0.64, a two-sided α risk of 5%, and a β risk of 20%. The key findings are summarized in Table 1. The interpretation of this trial is difficult because of the use of the factorial design, with inherent double randomization constituting the four arms. It is necessary to test first the assumption of equal relative risks for one randomization (ifosfamide: yes, *versus* no) compared across strata defined by the second randomization (MTP-PE: yes, *versus* no). In the first analysis, that is the primary analysis, the authors reported an interaction between the ifosfamide-based regimen and MTP addition on EFS. Owing to the interaction, the therapeutic role of the MTP added could not be appropriately determined [6]. In the second analysis published in 2008, the authors did not find an interaction between the ifosfamide-based regimen and MTP; however, although MTP addition failed to significantly improve EFS, it improved OS.

Table 1. Trials assessing maintenance therapy with immune-stimulating agents in patients with localized osteosarcoma.

Study	Bielack et al. [3]		Meyers et al. [5]	
Maintenance therapy	Switch		Continuation	
	IFNα-2b −	IFNα-2b +	MTP−	MTP+
n	359	357	172 + 167	168 + 170
3-year EFS	74%	77%	–	–
6-year EFS			61%	67%
Hazard ratio	0.83		0.80	
(95% CI), *p*	(0.61–1.12), $p = .214$		(0.62–1.0), $p = .08$	
5-year OS	81%	84%	–	–
6-year OS	–	–	70%	78%
Hazard ratio	0.77		0.71	
(95% CI), *p*	(0.50–1.19), $p =$ not done		(0.52–0.96), $p = .03$	

n: number of patients; EFS: event-free survival; OS: overall survival; 95% CI: 95% confidence interval, $p = p$-value.

Metronomic chemotherapy in high-risk rhabdomyosarcoma patients

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children and young adults. It has three histological subtypes: embryonal RMS (accounts for approximately 80% of pediatric RMS cases), alveolar RMS (accounts for approximately 15% pediatric RMS cases), and pleiomorphic RMS (the rarest form that develops in aged adults). Alveolar RMS is particularly aggressive. The survival of patients with non-metastatic RMS has been reported to be approximately 70% with the risk-adapted multimodal treatment strategy.

Metronomic chemotherapy consists of continuous administration of low-dose chemotherapy [7]. Cyclophosphamide (CTX) and vinorelbine (VIN) act as cytotoxic, antiangiogenic, and immune-stimulating agents when administered continuously at low doses [7,8]. Several exploratory trials have demonstrated the feasibility and the clinical activity of this combination in RMS patients with advanced and refractory disease [9,10].

Bisogno et al. reported the results of the RMS 2005 trial (NCT00339118). The trial included patients non-metastatic high-risk RMS with ages ranging from 6 months to 21 years [11]. High-risk RMS patients were defined as follows: patients with incompletely resected non-alveolar RMS (IRSII or III) at unfavorable sites with an unfavorable age ($\geq$10 years) or tumor size (>5 cm), or both; non-metastatic non-alveolar RMS with nodal involvement; and non-metastatic alveolar RMS but without nodal involvement. Patients in remission after standard treatment nine cycles of ifosfamide, vincristine, and dactinomycin with or without doxorubicin, and local treatment (radiotherapy with or without surgery) were randomly assigned (1:1) to follow-up or switch maintenance therapy to chemotherapy (six cycles of intravenous VIN 25 mg/m^2 on days 1, 8, and 15, and daily oral CTX 25 mg/m^2, on days 1–28). The primary endpoint was disease-free survival (DFS). The sample size was calculated based on the following assumptions: expected hazard ratio of 0.67, two-sided α risk of 5%, and β risk of 20%. Finally, 371 patients were enrolled (186 in the observation arm and 185 in the switch maintenance therapy arm). The key results are summarized in Table 2. The improvement in DFS did not meet the prespecified level of significance; nevertheless, the difference between both arms was clinically relevant. This trial is undoubtedly a trial that would change clinical practice since switch maintenance chemotherapy significantly improved the OS in this patient population.

Table 2. Switch maintenance therapy with cyclophosphamide and vinorelbine for localized high-risk rhabdomyosarcoma.

	Observation arm	Switch maintenance therapy arm
n	186	185
5-year DFS (ITT)	70%	78%
Hazard ratio		0.68
(95% CI), *p*		(0.45–1.02), $p = .061$
5-year OS (ITT)	74%	87%
Hazard ratio		0.52
(95% CI), *p*		(0.32–0.86), $p = .0097$
5-year DFS (PP)	70%	78%
Hazard ratio		0.67
(95% CI), *p*		(0.44–1.01), $p = .053$
5-year OS (PP)	74%	86%
Hazard ratio		0.53
(95% CI), *p*		(0.32–0.87), $p = 0.011$

n: number of patients, DFS: disease-free survival, OS: overall survival, ITT: intention-to-treat analysis; PP: per protocol analysis; 95% CI: 95% confidence interval, $p = p$-value.

Maintenance therapy in advanced stages

In advanced stages of different clinico-pathological entities, different maintenance therapies (e.g., metronomic chemotherapy, antiangiogenic agents, and molecularly targeted therapies) have been explored. Most of the related trials have been phase 1 trials, with a few being phase 3 trials.

Switch maintenance therapy with metronomic chemotherapy

Klingebiel et al. reported a randomized phase 2 trial in which the activity and safety of two approaches after first-line treatment for metastatic soft-tissue sarcoma in children and adolescents were assessed: high-dose chemotherapy *versus* oral metronomic chemotherapy [12]. The first-line treatment consisted of six cycles of alternatively administered ifosfamide-vincristine-actinomycin and carboplatin-epirubicin-vincristine. High-dose chemotherapy consisted of one cycle of CTX and thiotepa, a second cycle of melphalan and etoposide followed by stem cell infusion. In the other arm, metronomic chemotherapy was administered. It consisted of eight cycles in which four cycles of trofosfamide-etoposide (trofosfamide 2×75 mg/m^2/day during 10 days plus etoposide 2×25 mg/m^2/day during 10 days) and four cycles of trofosfamide-idarubicin (trofosfamide 2×75 mg/m^2/day during 10 days plus idarubicin 5 mg/m^2 on days 1, 4, 7, and 10) were alternatively administered. The key findings are summarized in Table 3. The interpretation of this trial is difficult since we are not able to distinguish the potential benefit of switch maintenance therapy from that of metronomic chemotherapy and the potential deleterious effect of high-dose chemotherapy. Furthermore, the induction treatment and the switch maintenance therapy are complex, the sample size calculation has not been explained, and compliance with the full protocol is low since the presented data described the outcomes of only 96 patients who completed the treatment, although 295 were registered in the trial.

Bevacizumab as continuation maintenance therapy

Angiogenesis plays a key role in sarcoma biology. The hypothesis that antiangiogenic agents could delay disease progression in advanced sarcoma patients is appealing. To the best of our knowledge, three trials have assessed the role of bevacizumab, a monoclonal antibody inhibiting vascular endothelial growth factor receptor, as continuation maintenance therapy after combination with chemotherapy.

Two trials focused on adult patients with soft-tissue sarcoma. First, D'Amado et al. reported a non-randomized two-stage phase 2 trial closed to recruitment after analysis of the first stage. Seventeen soft-tissue sarcoma patients (including 11 leiomyosarcoma patients) were enrolled to receive both doxorubicin and bevacizumab, followed by bevacizumab as

Table 3. High-dose chemotherapy *versus* metronomic chemotherapy after first-line chemotherapy in children with metastatic soft-tissue sarcoma.

	High-dose chemotherapy	Switch maintenance therapy	*p*
Total ($n = 96$)	$n = 45$	$n = 51$	–
5-year OS	27%	52%	.03
RMS patients, only ($n = 74$)	$n = 34$	$n = 40$	–
5-year OS	15%	52%	.001
Patients without bone or bone marrow involvement, only ($n = 51$)	$n = 20$	$n = 31$	–
5-year OS	40%	73%	.04

n: number of patients; OS: overall survival; *p*: *p*-value.

Table 4. Clinical trials assessing continuation maintenance therapy with bevacizumab in advanced soft-tissue sarcoma patients.

	Ray-Coquard et al. [14]		Chilsom et al. [15]	
Sarcomas	Advanced angiosarcoma		Advanced soft-tissue sarcoma	
			IVADo (4 cycles) then	
			IVA (5 cycles) then	
Standard arm	Weekly paclitaxel (6 cycles)		Maintenance chemotherapy	
	Bevacizumab –	Bevacizumab +	Bevacizumab –	Bevacizumab +
n	24	25	80	74
ORR	46%	28%	36%	54%
*m*edian PFS (months)	6.6	6.6	–	–
*m*edian EFS (months)	–	–	14.9	20.6
*m*edian OS (months)	19.5	15.9	–	–
Patients experiencing grade 3/4 toxicity	22%	44%	90%	94%

n: number of patients, ORR: best objective response rate; PFS: progression-free survival; EFS: event-free survival; OS: overall survival; IVADo: ifosfamide/vincristine/actinomycin/doxorubicin; IVA: ifosfamide/vincristine/actinomycin.

maintenance therapy. Only 5 out of the 17 patients (29%) received bevacizumab as maintenance therapy. The overall response rate was 12%. There were two instances of partial responses in two patients with leiomyosarcoma. The median time to progression was 8 months [13]. Ray-Coquard et al. reported a non-comparative randomized phase 2 trial assessing the addition of bevacizumab to weekly paclitaxel in patients with advanced angiosarcoma [14]. Angiosarcoma accounts for approximately 1% of all soft-tissue sarcomas. In the experimental arm, bevacizumab was administered during the chemotherapy and as maintenance therapy in patients with non-progressive disease. The primary aim was to estimate the activity of both regimens. The primary objective was the 6-month progression-free survival (PFS). Fifty patients were included. Bevacizumab was administered as maintenance therapy in eight (32.0%) of the 25 patients in the experimental arm. In both arms, 14 patients showed non-progression at 6 months. Other activity endpoints are summarized in Table 4. Grade 3 or 4 toxicities seemed more frequent in the combination arm. In both studies, bevacizumab was administered during chemotherapy, and a limited number of patients received bevacizumab as maintenance therapy because of rapid disease progression during combination treatment. These two trials do not suggest a major value of bevacizumab addition as maintenance therapy in soft-tissue sarcoma.

Chisholm et al. reported a large comparative randomized phase 2 trial assessing the addition of bevacizumab to chemotherapy in children and adolescent patients with metastatic sarcomas. The chemotherapy consisted of four cycles of ifosfamide/vincristine/actinomycin/doxorubicin (IVADo), followed by five cycles of ifosfamide/vincristine/actinomycin (IVA). Chemotherapy was followed by maintenance chemotherapy with metronomic CTX and vinorelbine. The patients were randomly assigned to receive either chemotherapy or chemotherapy plus bevacizumab. The primary objective was to improve EFS. The statistical hypothesis was as follows: hazard ratio of 0.57, two-sided α risk of 5%, and β risk of 20%. One hundred fifty-four patients were randomized to receive chemotherapy ($n = 80$) or bevacizumab plus chemotherapy ($n = 74$). The median EFS was 14.9 months with chemotherapy *versus* 20.6 months with chemotherapy plus bevacizumab; this difference in EFS did not reach the level of significance (HR = 0.93; 95% CI: 0.61–1.41; $p = .72$). There were no treatment-related deaths and no increase in the incidence of grade 3 or 4 toxicity in the combination arm (Table 4).

Switch maintenance therapy with an mTOR inhibitor

Intracellular signaling through the mammalian target of rapamycin (mTOR) and associated upstream signaling pathways are dysregulated in most sarcoma subtypes. Ridaforolimus (RIDA) is a non-prodrug analog of rapamycin (sirolimus) with high affinity for mTOR and optimized solubility, stability, and bioavailability. Owing to these pharmacological properties, RIDA was first evaluated as a treatment for advanced sarcomas in a non-randomized phase 2 trial [16]. A total of 212 heavily pretreated patients were enrolled; 61 patients (28.8%) achieved non-progressive disease at the best response. The best objective response rate (ORR) was 2%. The reported median PFS was 15.3 weeks and the median OS was 40 weeks.

In 2013, Demetri et al. reported a large double-blind phase 3 trial assessing the clinical benefit of switch maintenance therapy with oral RIDA in sarcoma patients showing

Table 5. Ridaforolimus as switch maintenance therapy in sarcoma patients showing non-progressive disease after the first-, second-, or third-line chemotherapy.

	Placebo	Ridaforolimus
n	364	347
Non-progressive disease at 4 months	29%	41%
p		$p < .001$
median PFS (1), months	14.6	17.7
Hazard ratio		0.72
(95% CI), *p*		(0.61–0.85), $p < .001$
median PFS (2), months	14.7	22.4
Hazard ratio		0.69
(95% CI), *p*		(0.58–0.81), $p < .001$
Median OS, months	85.3	90.6
Hazard ratio		0.93
(95% CI), *p*		(0.78–1.12), $p = .456$

n: number of patients, PFS: progression-free survival, OS: overall survival; 95% CI: 95% confidence interval, $p = p$-value, (1) PFS according to the central blinded review, (2) PFS according to investigator assessment.

stable disease or response after first-, second-, or third-line treatment for advanced disease [17]. The study population was heterogeneous, including patients aged 13 years or higher and soft-tissue (90%) and bone sarcoma (10%) patients regardless of the histological subtype. The primary objective was median PFS by a blinded central review. The sample size calculation was based on the following assumptions: expected hazard ratio of 0.75, β risk of 10%, and a two-sided α risk of 5%. Overall, 711 patients were randomly assigned to receive placebo (364) or RIDA (347). The key findings are summarized in Table 5. Technically, it was a positive superiority phase 3 trial meeting the primary objective since RIDA significantly improved the centrally-reviewed PFS. However, this trial failed to support the approval of the study drug since there was no improvement in OS and because the patients benefiting from RIDA were not clearly identified. The missing element was a validated predictive biomarker that could clearly target a subpopulation of patients benefiting from treatment with mTOR inhibitors as switch maintenance therapy.

Drug holiday in sarcoma patients

A drug holiday is a planned hold of active treatment to reduce toxicity in a palliative setting. This concept requires some prerequisites: the active drug is held before the development of unacceptable toxicity, the active drug does not cause cumulative toxicity that limits its administration, and the active drug provides a 'long-term' clinical benefit (at least stable disease). In daily practice, both referring physician and patient mutually agree to holding the treatment because the patient would like to rest some time, or make a summer break to meet with relatives, etc. To the best of our knowledge, the aggressiveness of sarcomas has been explored in a limited number of clinical trials, including two major randomized trials. We have excluded a randomized phase 2 trial with a discontinuation design that assessed the activity of regorafenib in soft-tissue sarcoma, since only eight patients were randomly assigned to continue or discontinue regorafenib after 12 weeks of administration [18].

Table 6. Trabectedin continuation *versus* drug holiday and rechallenge of in soft-tissue sarcoma patients showing controlled disease after six cycles of trabectedin.

	Continuation	Drug holiday
n	27	26
ORR	15%	11%
Median PFS, months	5.3	3.5
6-month PFS	48%	19%
Median OS, months	27.0	17.1
18-month OS	70%	44%
Q-TWIST, months	16.8	13.5

ORR: objective response rate; PFS: progression-free survival; OS: overall survival; Q-TWIST: quality-adjusted time without symptom and tumor progression.

Soft-tissue sarcoma and trabectedin drug holiday

Trabectedin is an alkylating agent prescribed for soft-tissue sarcoma patients. Some patients could receive a considerable number of cycles (e.g., 71 cycles over 6 years) before cumulative toxicity develops [19]. Le Cesne et al. reported the results of the T-Dis trial, a non-comparative randomized phase 2 trial with a discontinuation design (NCT01303094). In the T-Dis trial, patients first received up to six cycles of trabectedin and the patients who showed stable disease or response were randomly assigned to continue trabectedin until intolerance and disease progression or discontinue trabectedin (drug holiday) and then rechallenge at disease progression. The primary objective was to determine the 6-month PFS after randomization. In this exploratory phase 2 trial, there was no sample calculation, the aim was to randomize at least 50 patients. One hundred seventy-eight patients were enrolled in the first part of the trial; 53 patients were randomly assigned to continue ($n = 27$) or discontinue trabectedin ($n = 26$). Among 26 patients assigned to drug holidays, rechallenge with trabectedin was performed in 22 cases (85%). The data are summarized in Table 6 [20,21]. The sample size did not allow a formal comparison between the two arms; further, there was no quality-of-life analysis in this study. Nevertheless, quality-adjusted time without symptom and tumor progression (Q-TwisT) was calculated; Q-Twist was slightly better in the continuation arm, but this Q-Twist difference did not reach the level of significance [21]. Furthermore, there was a trend suggesting a benefit of continuation for OS; however, this clinically relevant difference did not reach the classical level of significance.

Gastrointestinal stromal tumor and imatinib drug holiday

Gastrointestinal stromal tumors (GISTs) are the most frequently developing sarcomas in adult humans. Approximately 85% of GISTs show activating mutation of c-Kit or platelet-derived growth factor receptor-α (PDGFR-α). Most of these activating mutations are sensitive to imatinib, a tyrosine kinase inhibitor. Imatinib is used as an adjuvant treatment, as preoperative treatment to obtain tumor shrinkage or as a first-line treatment at the metastatic stage. The median OS of metastatic GIST patients is approximately 6 years with imatinib therapy. Whether imatinib should be continued or discontinued after partial or complete response has been achieved remains debatable. Blay et al. reported

the results of a randomized trial with a discontinuation design in imatinib-treated GIST patients after 1 year [22] and then after 3 years (2010). In the initial design, the primary objective was the determination of the 1-year PFS. The statistical hypothesis was as follows: 1-year PFS of 90% with continuation, 1-year PFS of 75% with discontinuation, two-sided α and β of 10%. In the first part of the trial, 182 patients were enrolled and 58 were randomly assigned to continue (26) or discontinue (32) imatinib. The median PFS was 18 months in the continuation arm *versus* 6.1 months in the discontinuation arm ($p < .0001$). The OS was similar in both arms. Quality-of-life data were not analyzed because of excessive missing data [22]. Randomization was planned after 3 years of treatment; 434 patients were enrolled, 50 of whom were free of progression at 3 years and were randomly assigned to continue or discontinue treatment. After randomization, the 2-year PFS was 80% (95% CI: 58–91) in the continuation group and 16% (5–33) in the interruption group ($p < .0001$) [23].

Discussion

Overall, data about the clinical benefit of maintenance therapy or drug holiday in sarcoma management are limited. The use of immune-stimulating agents as maintenance therapy with IFNα in localized osteosarcoma failed to improve outcomes in a large phase 3 trial. The results of MTP adjuvant treatment in localized osteosarcoma are difficult to interpret. CTX and VIN as switch maintenance therapy for 6 months after chemotherapy for localized high-risk RMS must be considered as part of the standard of care since this metronomic chemotherapy significantly improves OS. The role of metronomic chemotherapy at an advanced stage has not been properly assessed. Bevacizumab continuation maintenance therapy failed to demonstrate a clinical benefit in advanced angiosarcoma, a paradigm of tumoral angiogenesis. Addition of bevacizumab to first-line treatment and switch maintenance therapy in children with advanced soft-tissue sarcoma failed to improve outcomes. Lastly, the mTOR inhibitor RIDA significantly improved the PFS in patients with advanced soft-tissue or bone sarcoma but without impacting the OS. Furthermore, predictive biomarkers to better target the population benefiting from switch maintenance therapy with an mTOR inhibitor are yet to be established. To conclude, the sole clinical setting in which maintenance therapy must be considered is high-risk localized RMS. Further clinical studies with a strong biological rationale and/or convincing data from phase 2 trials are necessary before maintenance therapy could be recommended in other settings.

We stress that CTX and VIN is an active regimen providing an objective response in RMS: ORR of 35–38% in two phase 2 trials [9,10]. On the contrary, RIDA provides a limited ORR of 2% in sarcoma patients [16]. Bevacizumab provided a short-term partial response in only 9% of angiosarcoma patients [24]. There are no published data demonstrating the activity of IFNα or MTP in osteosarcoma. These facts suggest that maintenance therapy could be effective if the selected regimen provides clear evidence of activity at the metastatic stage. Furthermore, the toxicity profile must be carefully considered. In case of advanced disease, the maintenance therapy administered to delay disease progression must be well tolerated and must not alter the quality of life. On the contrary, at the localized stage, maintenance therapy, which reinforces the therapeutic role of adjuvant or neoadjuvant classical chemotherapy, could be associated with more intense toxicity since the objective is to improve the curability of the disease.

Our systematic had some limitations, firstly this is not a meta-analysis focusing on one particular outcome, with the inherent bias analysis or sensitivity analysis. The limited number of published trials allows only a narrative description of the trial and a study-by-study discussion of the key-findings.

In the present review, we have summarized evidence based on fully published data. However, experts would be well aware that during the 2019 ASCO annual congress, the results of a large phase 3 trial assessing maintenance therapy with olaratumab were presented [25]. The primary aim of the ANNOUNCE Trial (NCT02451943) is to compare OS in an ITT population of advanced sarcoma patients. In this trial, patients have been randomly assigned to receive doxorubicin alone *versus* doxorubicin plus olaratumab followed by continuation maintenance therapy with olaratumab alone; 509 patients have been enrolled in the trial. The results are disappointing since the median OS was 20.4 *versus* 19.8 months (HR = 1.05, 95% CI: 0.84–1.30; $p = .69$) and the PFS was lower in the investigational arm in the ITT population (5.4 *versus* 6.8 m; HR = 1.23, 95% CI: 1.01–1.50; $p = .04$). These disappointing results did not confirm the results of the previously published randomized phase 2 trial that suggested a major benefit of olaratumab addition and maintenance therapy [25]. In the randomized phase 2 trial, 133 patients were enrolled, and the addition of and maintenance therapy with olaratumab was associated with a clinically relevant improvement in PFS (6.6 *versus* 4.1 months, $p = .0615$) and a statistically significant improvement in OS (26.5 *versus* 14.7 months, $p = .0003$) [26]. The difference in OS observed in the phase 2 trial could be explained by the imbalance in histological subtypes between both arms: tumor growth in the experimental arms was much slower. Nevertheless, we wish to stress that olaratumab, a PDGFR-α-blocking antibody, failed to demonstrate clinical activity in 14 GIST cases with PDGFR-α mutation [27].

Drug holiday or drug discontinuation has been explored in two settings: trabectedin treatment for metastatic soft-tissue sarcoma and imatinib treatment for GIST. In both settings, drug discontinuation led to rapid disease progression; however, there was no deleterious impact on OS. The main objective of a drug holiday is to reduce treatment-related toxicity and improve the quality of life. None of these 2 trials formally reported a quality-of-life analysis. Drug holidays could be assessed in other clinical settings; however, advanced sarcomas with a long-term stable disease status under treatment are rather rare. Therefore, at the time, regarding the aggressiveness of sarcomas, there were no strong data to support drug holidays in these clinical settings.

In conclusion, in this review, we summarized the findings of ongoing trials assessing strategies of maintenance therapy (See Supplementary Appendix). Most of the trials assessed the role of maintenance therapy with a multikinase inhibitor (e.g., pazopanib and regorafenib) or a chemotherapy agent without cumulative toxicity (e.g., trabectedin).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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