A novel approach to soft tissue sarcoma therapy: targeting tumor hypoxia

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Abstract

Single agent doxorubicin was introduced for the treatment of soft tissue sarcoma beginning in the 1970’s. Since then, combination therapies with an anthracycline backbone are commonly used, but have failed to show significant improvements in survival compared to single agent doxorubicin. TH-302, a pro-drug activated by tumor hypoxia, is a promising new therapeutic agent for soft tissue sarcomas. This novel agent has been shown to be safe in phase I and II clinical trials with minimal added toxicity. The data has suggested that TH-302 in addition to doxorubicin may have promising activity when compared to traditional combination therapy. A phase 3 study comparing TH-302 in addition to doxorubicin against doxorubicin alone has completed accrual. An improvement in outcomes would be proof of principal that targeting tumor hypoxia is an effective strategy for the treatment of soft tissue sarcoma.

Keywords: Soft tissue sarcoma, TH-302, chemotherapy, sarcoma, targeted therapy

Introduction

Over the last 30 years there have been numerous advances in the treatment of localized soft tissue sarcoma (STS). In the early 1970’s Steven Rosenberg heralded the age of neoadjuvant chemotherapy and limb salvage therapy for sarcomas [1,2]. As a result, the amputation rates in STS have decreased from over 50% to less than 5%. Limb salvage surgery in combination with pre or post-operative radiation therapy with/without chemotherapy is now the standard approach for localized disease and has helped improve the quality of life for many patients [3].

Unfortunately, we have been unable to similarly improve the outlook of patients with metastatic soft tissue sarcomas. These malignancies represent 1% of all cancers and in the United States. In 2014, approximately 12,020 people were diagnosed with soft tissue sarcoma and 4,740 people will have expired from this disease [4,5]. Despite our best treatments, 10-year survival from when there has been distant disease spread is still less than 10% [6]. Our current approach to the treatment of soft tissue sarcomas was developed in the 1970’s with the introduction of single agent doxorubicin [7]. Since then, combination therapies including various combinations of anthracyclines with ifosfamide have been approved and are commonly used, but have failed to show significant improvements in survival compared to doxorubicin alone [8,9]. Recently, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, pazopanib (Votrient), was approved for the treatment of advanced soft tissue sarcoma that has failed standard chemotherapy [10]. This novel therapy has demonstrated an improvement in progression free survival but has not yet been shown to improve overall survival. Unfortunately, there is an immediate need to develop new therapies for soft tissue sarcomas.

In this paper, we will review current concepts in the medical management of soft tissue sarcomas.

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We will discuss recently published studies and place them into the context of how physicians are treating this disease. Excerpts from published manuscripts will be presented that discuss novel targets and current treatment strategies. Finally, a new therapeutic, TH-302, will be introduced. The concept of tumor hypoxia and its relevance to soft tissue sarcomas will be described. We will review its clinical development and discuss early findings regarding its activity and side effect profile.

Review
Current treatments for soft tissue sarcoma

Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise approximately one percent of all adult malignancies [4]. The majorities of sarcomas originate from the muscle, fat, and fibrous tissue (as opposed to bone) and are classified as soft-tissue sarcomas [11]. According to the World Health organization classification system, soft-tissue sarcoma includes more than 100 different histologic types [12]. Undifferentiated is the most common sub-type followed by unclassified, liposarcoma, leiomyosarcoma, and synovial sarcoma (see Table 1). The behavior and biology of these subtypes are quite variable. Therefore, the sub-classification of sarcomas is very important to select the best therapies.

Appropriate treatment for soft tissue sarcoma depends on both patient and tumor characteristics. Patient age and performance status are predictors for outcomes with systemic therapy [13] and important for selecting the appropriate intensity of treatment [14]. Tumor size, histologic grade, and stage of the tumor are also critical when selecting therapeutic approaches [15]. Low-grade and local tumors are usually treated with surgery, whereas higher-grade and advanced disease is treated with chemotherapy, either alone or in combination with radiation and/or surgery.

In our clinical practice, optimal approaches to the treatment of advanced soft tissue sarcoma depend on histopathologic characteristics of the tumor. Pleomorphic sarcomas are treated with doxorubicin based regimens, either single agent, or combined with ifosfamide. Leiomyosarcomas, particularly of uterine origin, are treated with a combination of gemcitabine and docetaxel in the first line [16,17]. Synovial sarcomas are very responsive to ifosfamide and are treated accordingly [18]. Liposarcomas are treated based on subtype classification [19]. Dedifferentiated liposarcoma do not respond well to chemotherapy and should be enrolled in clinical trials [20]. High-grade pleomorphic liposarcomas are treated with chemotherapy. Well-differentiated liposarcomas are usually approached surgically and are chemoresistant. Patients with myxoid liposarcomas are often directed to clinical trials with Trabectedin [21]. Trabectedin is a marine-derived anti-tumoral agent approved in Europe for sarcoma, but currently unavailable in the United States outside of a protocol.

Chemotherapeutic agents used in soft tissue sarcoma

Doxorubicin, an anthracycline chemotherapeutic agent, mechanisms of action include intercalating DNA and RNA base pairs, inhibiting topoisomerase II complex, creating oxygen free radicals, and inducing histone eviction of DNA strands. Initially studied in soft tissue sarcomas in 1970’s, doxorubicin as a single agent is the standard treatment of advanced sarcoma with improved progression free and overall survival [22]. The side effects associated with doxorubicin include reversible bone marrow suppression, mouth sores, hair-loss, nausea and vomiting, and both acute and chronic cardiotoxicity. Multiple studies have investigated the dose and schedule of doxorubicin. The current accepted approach is between 60-75mg/m² given as an IV bolus or continuous infusion [23]. The standard of care is to deliver 75mg/m² as an IV bolus.

Ifosfamide was first synthesized in the 1960's and is a member of the oxazaphosphorine family of alkylating agents [24,25]. It is a chemical modification of cyclophosphamide, with varying

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<td>Gastrointestinal stromal tumors (GIST)</td>
<td>Derived from the gastrointestinal tract and express CD-117 and overexpress cKIT. These tumors are treated with Gleevec, a cKIT tyrosine kinase inhibitor.</td>
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position of its two chloroethyl groups on the central ring, that provides a structure with greater antitumor activity and a better toxicity profile [26]. Response is dose dependent as was described by Le Cesne et al., in 1995 [24]. However, doses are often limited by toxicities, which include hemorrhagic cystitis, renal tubular acidosis, salt wasting nephropathy, and central nervous system toxicity that can cause seizures and death [25]. Continuous infusion of ifosfamide has been shown to decrease toxicity when compared to bolus administration [26,27]. Doxorubicin and ifosfamide, comprise the standard chemotherapy regimens for soft tissue sarcoma, have consistent response rates of 10%–25% as single agents [9,24,29].

Combination regimens have been used for advanced soft tissue sarcoma, as they are associated with improved response rates. Unfortunately, in soft tissue sarcoma, chemotherapeutic response does not correlate with prolonged survival [13,30]. Combination regimens including AIM (doxorubicin, ifosfamide, and mesna) and MAID (mesna, doxorubicin, ifosfamide and dacarbazine) when compared to single agent doxorubicin showed a modest progression free survival but no overall survival benefit [31]. As a result, single agent adriamycin is accepted as the standard first line regimen for advanced soft tissue sarcoma. A recent EORTC study has reconfirmed that doxorubicin is the standard of care for the treatment of soft tissue sarcoma [9]. Although combination therapy with doxorubicin and high dose ifosfamide is associated with a higher response rate it did not improve outcomes [9].

Combination regimens adding cytotoxic agents to a gemcitabine backbone are also commonly used in the treatment of soft tissue sarcomas. In a randomized phase 2 study, gemcitabine and docetaxel was compared to gemcitabine alone [16]. This combination regimen proved superior in response rate, progression free survival, and overall survival. Patients with leiomyosarcomas of the uterus and undifferentiated sarcomas had the most benefit from this approach. Combination regimens of gemcitabine in addition to vinorelbine or dacarbazine have also been explored and are acceptable approaches [32,33].

Trabectedin, or Yondelis, is a novel alkaloid from the Caribbean tunicate Ecteinascidiaturbinate. Having a unique mechanism of action, trabectedin binds to the minor groove and induces DNA damage that alters transcription and other essential processes [34]. It is approved for the second line treatment of soft tissue sarcomas since 2007 by the European Medicine Agency. Several clinical trials have confirmed extended disease stability rates in soft tissue sarcomas, especially leiomyosarcoma, and marked response rates in myxoid liposarcomas [35,36]. In the US, there are ongoing registration trials comparing trabectedin to dacarbazine in secondline therapy for leiomyosarcoma and liposarcomas that have failed treatment with an anthracycline (ClinicalTrials.gov Identifier:NCT01343277). A new drug application with the FDA was recently filed for its use in second line therapy for advanced soft tissue sarcomas.

The newest medication approved for the treatment of soft tissue sarcoma is not a traditional chemotherapeutic agent but a tyrosine kinase inhibitor. In 2012, pazopanib was FDA approved for the treatment of metastatic non-adipocytic soft tissue sarcoma in patients that had failed standard chemotherapy. Pazopanib retards the activity of the vascular endothelial growth factor (VEGF) receptor and the platelet derived growth factor (PDGF) receptor amongst others [37,38]. In the registration study, all grades of soft tissue sarcomas were included and adipocytic tumors and gastrointestinal stromal tumors were excluded. It is notable that this drug was able to improve progression free but not overall survival. Only 6% of the patients had a partial response and there were no complete responses. Although this therapy does provide an option for advanced patients it does not lead to dramatically improved outcomes for patients with soft tissue sarcomas.

Successful new therapies for the treatment of soft tissue sarcoma will either target genetic abnormalities or exploit biologic characteristics unique to this disease. Several sarcomas have chromosomal translocations, gain of function mutations, and gene amplifications that are not only diagnostic but provide rational targets for new therapies (see Table 2). These tumors are also characterized by upregulated angiogenesis, mesenchymal to epithelial transition, and tumor hypoxia [39]. Targeted therapies will hopefully lead to more effective options with decreased side effects.

**TH-302: A new concept in systemic therapy**

TH-302 is a 2-nitroimidazole prodrug of a brominated form of isophosphoramide mustard developed by Threshold Pharmaceuticals (Figure 1) [40]. TH-302 requires conversion into its active metabolite (dibromoisophosphoramide) in hypoxic environments via intracellular electron reductases. TH-302 is effective at hypoxic conditions typical of tumor microenvironース but not in aerobic conditions. TH-302 shows promise in angiogenesis inhibition and is currently being evaluated in phase II trials for metastatic melanoma and renal cell carcinoma.

**Table 2. Novel pathways and molecular targets for the treatment of sarcoma.**

<table>
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<tr>
<th>Sarcoma subtype</th>
<th>Molecular target</th>
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<tr>
<td>De-differentiated liposarcoma</td>
<td>Murine double minute gene (MDM2) and cyclin-dependent kinase 4 (CDK4) amplification</td>
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<tr>
<td>Myxoid liposarcoma</td>
<td>FUS-CHOP gene fusion oncoprotein</td>
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<tr>
<td>Solitary fibrous tumors</td>
<td>NAB2-STAT6 gene fusion oncoprotein</td>
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<tr>
<td>Synovial sarcoma</td>
<td>SYT-SSX gene fusion oncoprotein</td>
<td></td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>PAX3-FOXO1 (P3F) gene fusion oncoprotein</td>
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<tr>
<td>Angiosarcoma</td>
<td>Angiopoetin-TIE2 pathway</td>
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<tr>
<td>Malignant peripheral sheath tumors</td>
<td>mTOR pathway</td>
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There are over 100 different subtypes of bone and soft tissue sarcomas. Soft tissue sarcomas as a class of tumors have a low response rate to chemotherapies and each subtype responds differently to chemotherapy. The tumor biology of each sarcoma subtype is different making the development of histologically driven or pathway-specific targeted therapies key to the future of soft tissue sarcoma treatment. Below are a number of novel molecular targets for specific subtypes of sarcomas that could prove to be useful in the future of sarcoma treatment.
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not the only hypoxia-activated prodrug to be developed; others have been studied but are not currently being used given their less-favorable risk-benefit ratio. These studies have revealed several properties that are required for a successful drug in this class. Most importantly, these drugs must penetrate and diffuse within the hypoxic area and the pro-drug activation has to occur at an oxygen level that minimizes off-target effects and damage to normoxic tissue [41].

**Targeting tumor hypoxia in soft tissue sarcoma**

Tumor hypoxia is also well established as a poor prognostic factor for malignancies [42]. Tumors with increased hypoxia are less likely to respond to chemotherapy and more likely to metastasize [41]. Most tumor types contain areas of hypoxia to varying degrees [43]. Sarcomas, uniquely more than other tumor types, are characterized as hypoxic and containing necrotic center [44,45]. These findings have been confirmed radiographically with positron emission tomography (PET) imaging with fluorine-18 fluoromisonidazole (FMISO) [46]. The biologic consequences of tumor hypoxia include: selecting tumor genotypes that are resistant to hypoxia, increased angiogenesis and receptor tyrosine kinase signaling, and increased expression of drug resistance proteins [43]. Hypoxia in sarcomas leads to increased expression of hypoxia inducible factor [44] and vascular endothelial growth factor [47], which leads to increased metastatic potential. Chemotherapy resistance is promulgated through stromal proliferation and other micro-environmental changes causing aberrant cell-cell and cell-stroma interactions [48]. This leads to phenotypic changes and resistance to treatment.

A drug such as TH-302, which has been shown to have little cytotoxic effect in normal oxygen environments and high cytotoxic effect in hypoxic regions, theoretically provides a tumor specific therapeutic (see Figure 2) [40,41].

Once activated in tumor hypoxia, TH-302 will penetrate into surrounding tissues and has activity in both hypoxic and oxygenated areas of the tumor [49]. In pre-clinical studies, this chemotherapeutic was able to enhance the activity of adriamycin in the perivascular as well as hypoxic areas [50]. This therapy has shown activity in both phase I and II trials for soft tissue sarcomas, melanoma, and pancreatic cancer [51]. Increased activity with an acceptable safety profile is proof of principle that tumor hypoxia can be used to selectively target cancer cells.

**TH-302 clinical development for sarcomas**

A phase I study of TH-302 in solid tumors was completed and presented in 2011. 57 patients were enrolled among whom 37 received TH-302 from 7.5mg/m² to 670mg/m² and 27 patients received TH-302 in dosages ranging from 670mg/m² to 940mg/m² given as an weekly intravenous infusion [52]. The most common adverse effects of any grade included nausea, vomiting, fatigue, anemia, and low white blood cell count. Less common adverse effects were mouth sores, fevers, dehydration, constipation, neutropenia, and thrombocytopenia. The dose limiting toxicity was skin and mucosal side effects.

Another phase I study with combination doxorubicin and TH-302 in soft tissue sarcoma was reported by Ganjoo et al., in 2011 [53]. Sixteen patients with advanced soft tissue sarcoma were enrolled and administered doxorubicin 75mg/m² on day 1 of a 21 weeks cycle. TH-302 was administered on day 1and day 8 of the 3-week cycle with an initial dosage of 240mg/m², which was increased using a 3+3 design. Common...
side effects included fatigue, nausea, and skin rash. Low blood counts were the dose limiting toxicities despite the addition of prophylactic growth factors. The maximal tolerable dose was determined to be 300mg/m² of TH-302 when combined with doxorubicin. The combination therapy was found to be reasonably safe with limited additional toxicity and the study was expanded to include a phase II component to investigate the combination of doxorubicin and TH-302 at the established maximum tolerated dose.

In the phase 2 TH-302 study, patients with metastatic soft tissue sarcoma received doxorubicin at 75mg/m² every three weeks and TH-302 (300mg/m² on days 1 and 8 of a 21-day cycle) [54]. After six cycles, patients with stable disease, partial or complete responses, and with acceptable toxicity, were eligible to receive TH-302 maintenance therapy. Median progression free survival (PFS) and median overall survival was 6.5 months (95% CI, 5.8 to 7.7 months) and 21.5 months (95% CI, 16.0 to 26.2 months) respectively. Best tumor responses were complete response (N=2 [2%]) and partial response (N=30 [34%]). Overall best response (partial and complete responses, unconfirmed) of 36% and clinical benefit rate of 84% (CR+PR+Stable Disease) were noted, see Figure 3.

The results for TH-302 single agent maintenance therapy population (N=48) were also provocative. In this single arm study, during TH-302 maintenance (N=48), five patients improved from stable disease to partial response, and one patient improved from partial to complete response. It is difficult to determine whether this represents a delayed response to doxorubicin or if it points to a role for TH-302 in the maintenance setting. This should be investigated further.

The toxicity profile of this agent is related to its mechanism of action. The epidermis and superficial mucosa contain areas of relative hypoxia and TH-302 causes hand foot rash, mucositis, and intertriginous rash [55]. Guidelines have been published to help manage and reduce this toxicity. Interestingly, applying cold packs and ice-chips to the skin and oral cavity have been shown to help mitigate TH-302 toxicity. Presumably, vasoconstriction associated with cryotherapy helps reduce exposure to the drug. In addition, moisturizers and other emollients are recommended to help reduce the hand-foot syndrome and rashes.

The early results from the TH-302 studies appear promising when compared to common chemotherapy regimens used today including MAID, AIM, and AD which have response rates of 15-30% as well as a median overall survival of 13-14 months [8,56-58]. The side effects associated with the treatment are tolerable. As a result of these data phase III trials were initiated.

The “TH-CR-406 trial” is a phase III trial of TH-302 in combination with doxorubicin in soft tissue sarcoma. This trial opened for enrollment in September 2011 and completed enrollment in January 2014. Eligible patients include those with any advanced or metastatic sarcoma for which doxorubicin would be an appropriate therapy, including synovial sarcoma, undifferentiated sarcoma, liposarcoma (other than well differentiated), leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, pleomorphic rhabdomyosarcoma, myxofibrosarcoma, epithelioid sarcoma, and undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (see Table 3). Patients are randomized to doxorubicin single agent therapy (75mg/m² Day-1 every 21 days) or doxorubicin combined with TH-302 (300mg/m² Day-1 and 8, every 21 days). Patients randomized to TH-302 continued maintenance therapy after 6 cycles of doxorubicin. The primary end point is overall survival and secondary end points are progression free survival, duration of response, and toxicities.

This is an international study with sites open in Belgium, Canada, Germany, Israel, Italy, Hungary, Poland, Spain and United States,Austria, Denmark, France and Russia. There is a planned futility analysis (113 events) projected to occur soon. Primary analysis (323 deaths) projected for 2015.

Conclusions

Patients with advanced or metastatic soft tissue sarcomas have limited options in therapy. Since the advent of doxorubicin in the 1970’s, there have been no further advances prolonging overall survival in metastatic soft tissue sarcoma in adult patients. Combination chemotherapeutic regimens and targeted agents to date have only shown progression free survival benefit with no proven overall survival benefit when compared to single agent doxorubicin.

TH-302 is a promising new therapeutic agent for soft tissue sarcomas. This novel agent, in combination with doxorubicin, has been shown to be safe with promising activity in phase I and II trials.
Table 3. Soft tissue sarcoma subtypes included in TH-406 study.

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<td>Myxofibrosarcoma</td>
<td>Malignant fibrous histiocytoma (MFH) is a soft tissue neoplasm, composed of cells sharing fibroblastic and histiocytic features. MFH is one of the most aggressive of the group of fibrohistiocytic tumors. MFH exhibits a high local recurrence rate and a significant metastatic rate. It is more common in adults and especially the elderly.</td>
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As defined by the World Health Organization (WHO), soft tissue sarcomas include more than 100 different histologic subtypes. These are the subtypes that were included in this clinical trial.

clinical trials. A phase III trial is currently underway comparing doxorubicin with the combination of doxorubicin and TH-302. Interim analysis is expected in 2015.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors participated in drafting the article and revising it critically for important intellectual content; and gave final approval of the version to be submitted.

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