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Targeted Treatment of Soft-Tissue Sarcoma

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Research Article

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ABSTRACT

Background: Soft-Tissue Sarcoma (STS) is a heterogeneous group of sarcomas with a low incidence. The treatment of advanced disease is poor, and the mortality is high. In other types of cancer, targeted treatment has shown promising results. Therefore, we aimed to generate an overview of the clinical experiences with targeted treatments based on a pre-specified target in patients with STS.

Methods: A systematic literature search was conducted in PubMed and Embase databases. The programs ENDNOTE and COVIDENCE were used for data management. The literature was screened to assess the article's eligibility for inclusion. A total of 31 articles were included in this review.

Results: Twenty-eight targeted agents were used in the treatment of 80 patients with advanced STS and a known pre-specified genetic alteration. MDM2-inhibitors were the most studied drug (n=19), followed by crizotinib (n=9), ceritinib (n=8) and 90Y-OTSA (n=8). All patients treated with MDM2 inhibitor achieved a treatment response of Stable Disease (SD) or better with treatment duration of 4 to 83 months. For the remaining drugs, a more mixed response was observed. The evidence is low since most studies were case reports or cohort studies, where only a few STS patients were included.

Conclusion: Many targeted agents are available that can precisely target specific genetic alterations in advanced STS. The MDM2 inhibitor has shown promising results and must be considered in patients with MDM2 amplification; however, further investigation is needed to identify the potential survival effect of targeted treatment in sarcoma.

Keywords: Targeted treatment; Gene mutations; Sarcoma; MDM2 amplification

INTRODUCTION

Sarcomas are neoplasms originating from the connective tissue. With more than eighty histological subtypes, sarcomas are highly heterogeneous and rare as they only represent about one to two per cent of all adult cancers [1,2]. Overall, sarcomas are divided into Soft-Tissue Sarcoma (STS), representing approximately 84% of sarcoma patients, and sarcomas arising from bone and cartilage, representing approximately 16% of the patients [3]. The standard treatment of localized disease is surgery, with or without radiotherapy [4]. Despite a curative intended therapy, the prognosis is grave as twenty-five per cent of the patients will develop metastatic disease. These patients are primarily treated with chemotherapy [5,6]. However, the response to chemotherapy is low, and the mortality is high. Therefore, the need for improved treatment for patients with advanced STS is wanted. Over the past decades, there have been identified multiple genetic alterations in cancer. This has revolutionized the treatment by enabling targeted treatment to precisely inhibit the growth and progression of cancer cells [7]. In STS, the frequency of genetic alterations is between 84%-91%, with the most frequently altered genes being TP^{53}, ATRX, RB1, PTEN, MDM2, CDK4 and CDKN2A/ B [8-14]. Different genetic alterations can enable targeted therapy in patients suffering from advanced STS. However, currently, no overview covering treatment options against specific genetic alterations in STS exists. This systematic review aims to generate an overview of the clinical experiences with targeted treatments based on a pre-specified target in patients with STS.

MATERIALS AND METHODS

Data sources and search strings

A systematic review of the existing literature investigating the targeted treatment of adult STS was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [15]. A comprehensive literature search in the medical databases PubMed and Embase was conducted on the 1st of April 2022. The following filters were used in both databases: “not animals” and “English”. There was no time restriction. The search strings used are presented in Table 1.

Table 1. Presentation of the search strings.

Database	Search strings	Number of results
Pubmed	("Sarcoma"[MeSH Terms] OR "soft tissue sarcoma*"[Text Word] OR "soft tissue neoplasm*"[Text Word]) AND ("adult*"[Text Word] OR "Adult"[MeSH Terms]) AND ("Molecular Targeted Therapy"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] OR "molecular targeted therapy*"[Text Word] OR "immunotherapy*"[Text Word] OR "targeted therapy*"[Text Word])	846
Embase	('sarcoma'/exp OR sarcoma*:ab,kw,ti OR 'soft tissue sarcoma*':ab,kw,ti OR 'soft tissue neoplasm*':ab,kw,ti) AND ('adult'/exp OR adult*:ab,kw,ti) AND ('molecularly targeted therapy'/exp OR 'molecularly targeted therapy*':ab,kw,ti OR 'immunotherapy'/exp OR immunotherapy*:ab,kw,ti OR 'targeted therapy*':ab,kw,ti) AND [humans]/lim AND [english]/lim	3150
Note: GA: Genetic Alteration; STS: Soft-Tissue Sarcoma; TT: Targeted Treatment; *: Involves PubMed search criteria		

Study selections

The inclusion criteria were as follows: (I) original data, (II) the patients had to have a proven pathological STS with a specific genetic alteration prior to therapy with a targeted drug, (III) treatment outcome of one or several targeted agents had to be presented, (IV), if a study also included other types of cancer, the treatment outcome on STS had to be presented separately, (V) the patients had to be older than 15 years old, (VI) if a study included both paediatric and adult STS, the treatment outcome regarding adult STS had to be presented separately. Exclusion criteria were as follows: (I) non-English articles, (II) conference abstracts, (III) animal or in vitro studies, (IV) bone or cartilage sarcomas, hemopoietic sarcomas and sarcomatoid tumours, (V) results only presented in figures, (VI) studies regarding immunotherapy.

Data extraction and quality assessment

All titles and abstracts were screened to identify eligible articles. To validate the above-mentioned in- and exclusion criteria, one hundred studies were randomly selected and screened independently by all four authors. Any disagreement was resolved by consensus. Two of the authors (AIR, VNM) screened the rest of the titles and abstract. In case of disagreement, conflicts were resolved by all four authors.

After identification of eligible full-texts, ten randomly selected articles were read by three authors (AIR, BSP, and NAP) and subsequently included or excluded. The rest were included or excluded through full-text reading by one author (AIR) and, in case of doubt, discussed by the other authors until consensus was reached. Covidence and Endnote (Clarivate Analytics) were used for duplicate and reference management during the inclusion and exclusion process. The protocol was submitted to the PROSPERO database (CRD42021252341).

One author (AIR) performed data extraction, which subsequently was checked by the other authors. Data extraction included: the name of the first author, year of publishing, study design, the genetic alteration that served as a target, the type and/or name of the targeted drug, population and treatment outcome. Studies included in this systematic review were quality scored by all authors using the Quality assessment tools for Case Series Studies and the Quality assessment tools for Observational Cohort and Cross-Sectional Studies, National Institute of Health, USA.

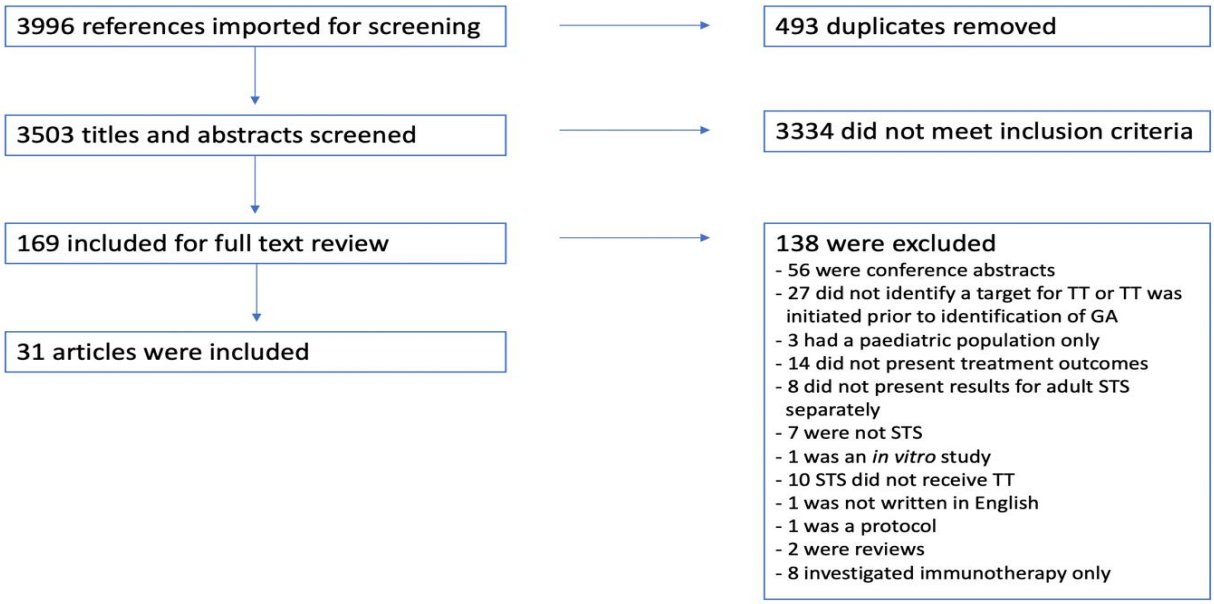
The studies were rated “good”, “fairly” or “poor” according to the estimated risk of bias. All authors performed the quality assessment, and any disagreements were solved by consensus. Due to the heterogeneity of the studies and the many different outcomes they used, a meta-analysis could not be performed.

RESULTS AND DISCUSSION

Study selection

A total of 3996 titles and abstracts were identified using the two search strings presented in Table 1. After duplication screening, 493 duplicates were removed, resulting in 3503 unique hits. All titles and abstracts were screened, and subsequently, 169 full texts were read, returning 31 articles that met the above-mentioned inclusion and exclusion criteria and thus, were included in this systematic review. The in-and exclusion process is presented in Figure 1.

Figure 1. A flow chart presenting the in- and exclusion process.



Study description and quality assessment

Study characteristics for all included studies are presented in supplementary Table 2. All studies were either case reports (n=17) or cohort studies (n=14). In addition, an update of a case report was identified, and the sum of the two identified case reports was included [16,17]. The articles were published between 2015 and 2021. In total, eighty patients representing 30 different histological subtypes were treated with targeted therapy based on a pre-specified target. Twenty-eight different drugs were used, targeting 41 different targets. Fourteen patients received two or more different targeted agents in the same treatment course. Thirteen of the drugs were only given to one patient.

Twelve case reports were rated good, and the last five were rated fairly. Eleven cohort studies were rated good, two fairly and the last poor. The treatment effect on patients with advanced STS was measured by nine different treatment outcomes: Complete Response (CR), the median time to progression, No Evidence of Disease (NED), Overall Survival (OS), Partial Response (PR), Progression-Free Survival (PFS), Progressive Disease (PD), relapse-free survival and Stable Disease (SD). Only MDM2-inhibitor (n=19), crizotinib (n=15), ceritinib (n=8) and 90Y-OTSA (n=8) were given to eight or more patients. All patients receiving MDM2-inhibitors were patients with liposarcoma and MDM2 amplification; furthermore, all patients had a treatment effect of SD or better with a treatment duration ranging from 4 to 83 months [18]. The patients receiving crizotinib had NTRK1 fusions (n=2), ALK rearrangements (n=9), ROS1 mutations (n=3) or MET mutation (n=1) and achieved varying responses from PD to CR with a treatment duration ranging from three months to two years [19-24]. The patients receiving ceritinib had ALK rearrangements (n=6), ROS1 amplification (n=1) or IGFR1 amplification (n=1) and achieved varying response from PD to PR with a treatment duration of up to 24 months [25,26]. Eight patients with FZD10 expression received the targeted radioactive drug 90Y-OTSA. Three patients received 370 MBq of these; one patient had SD and two patients PD. Five patients received 1100 MBq two patients had SD, and three had PD. One of the patients with SD receiving 1100 MB1 90Y-OTSA also got a second injection that resulted in PFS for 21.4 weeks [27].

In total, seven patients achieved CR, near CR or NED. The patients achieving CR were treated as follows: Three patients received crizotinib targeting an NTRK1-KHDRBS1 fusion, ALK-rearrangements or an LMNA-NTRK1 fusion; one patient received MDM2-inhibitor, targeting an MDM2-amplification and one patient received larotrectinib against a SPECC1L-NTRK3 fusion [28,29]. The two patients achieving NED received crizotinib against ALK expression and a SLC12A1-ROS1 fusion, respectively [30-44].

Advanced sarcoma is a rare but severe disease, and the need for better treatment options is highly wanted. We have conducted a systematic review to cover targeted treatment given to patients suffering from advanced STS with a known genetic alteration. The use of targeted treatment in STS is still on an individual and experimental level. Most of the studies included in this systematic review were case reports or cohort studies where only a few individuals suffering from advanced STS were included. Summarised, eighty patients received 28 different targeted drugs. Thirty different subtypes of STS received targeted treatment, and among them, 41 different genetic alterations were identified. Thus, several targeted agents were administered to patients with different kinds of advanced STS but with highly variable results.

Several studies have shown that there exist many different genetic alterations in STS. Groisberg et al. found that 93 out of 102 advanced STS patients had at least one genetic alteration where the most frequent were found in TP53, CDK4 and MDM2, and 61% had a potentially targetable alteration. However, only 16% of the patients received a targeted drug. Similar observations were found by Lucchesi et al. [12,13] where 84% of the 584 included STS patients enharboured a genetic alteration. Furthermore, the most frequent mutations were observed in TP53, MDM2 and CDK4, and 41% of the patients had at least one potentially targetable alteration. Gusho et al. also found a high frequency of genetic alterations with at least one genetic alteration in 122 out of 136 samples. The most frequent mutations observed were in TP53, CDKN2A/B and RB1, and 47% had a potentially targetable mutation [12].

In this review, all patients receiving MDM2-inhibitors had liposarcomas, with treatment response of SD or better, including one CR. MDM2 amplification is a common genetic alteration in STS. Three studies have shown a prevalence of 5%, 22% and 40% in STS. In specific subtypes of STS, the prevalence is even higher. In well-differentiated and dedifferentiated liposarcoma, the amplification of 12q13-15 is common, resulting in the amplification of the MDM2 gene. Studies have shown that over 90% of these sarcomas have MDM2-amplification. Because of the high prevalence of MDM2 alterations in STS, especially in liposarcoma, and the reports with high clinical effect, targeting this specific alteration must be considered. Crizotinib was given to patients with mutations in ALK, ROS1, MET or NTRK1. There were varying treatment responses, but three out of nine patients had CR or near-CR, and two patients had NED; therefore, they had an overall survival benefit. One of the patients with CR had ALK gene rearrangements, and the other had NTRK1-KHDRBS1 fusion. The patient with a near-CR response had an LMNA-NTRK1 fusion. The patients with NED had high ALK expression and a SLC12A1-ROS1 fusion, respectively. Owed to the aim of this study, only patients receiving treatments targeting a known specific target was included. Therefore, only seven of the included patients received pazopanib, a multitarget tyrosine-kinase inhibitor; however, the drug is given to far more patients suffering from advanced STS. Even though studies exist on pazopanib in STS, these studies were not included as they did not have a specific pathological proven target prior to treatment with pazopanib. Many of these studies showed a treatment effect on STS without prior identification of a specific genetic alteration. MDM2-inhibitors, crizotinib, ceritinib and 90Y-OTSA were given to most patients. However, the overall population receiving targeted therapy is so tiny that it is difficult to conclude the overall survival effect of the targeted agents used. Furthermore,

nine different treatment outcomes were used to measure the effectiveness of the drugs, making it challenging to conduct a meta-analysis to investigate the potential survival effect of agents on advanced STS. The majority of the included patients were previously treated with curative intended treatments, and many had one or more treatment courses with chemotherapy. Furthermore, targeted agents were tried as a last resort for patients with advanced STS. Maybe, if targeted therapy was introduced to the patients before relapse occurred, the patients might have had a more substantial benefit from the treatment and more prolonged survival. It would have been interesting to compare targeted treatment against chemotherapy as the first-line treatment for advanced STS to see if there is a difference. Larger studies are needed to investigate the potential effect of targeted therapy on STS, e.g. case/control studies, where targeted treatment is compared to chemotherapy, and ultimately randomized controlled trials.

The strengths of this systematic review are the comprehensive systematic review of the available literature on targeted treatment of STS in two major medical databases. Broad search strings and in- and exclusion criteria were used to avoid missing relevant articles. Two authors screened the literature, and all authors validated the in- and exclusion criteria. Nonetheless, this review also has its limitations.

CONCLUSION

During the last decades, many genetic alterations in STS have been identified, enabling the use of targeted treatment. This systematic review revealed many studies regarding genetic alterations and targeted treatment in advanced STS. Twenty-eight targeted agents have currently been tried in advanced STS. However, most articles are case reports and cohort studies representing only a few patients with advanced STS. Studies comparing targeted treatment to chemotherapy in case/control studies and ultimately randomized controlled trials can make it easier to investigate the potential survival benefit that targeted agents can provide to patients suffering from advanced STS. All the studies included are either case reports or cohort studies, where only a few patients have advanced STS. The studies used many different measures of outcome. One of the exclusion criteria was non-English articles, and it is possible that other studies concerning the same topic were written in other languages. Thus, language bias cannot be excluded.

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