Recommendations for Treatment with Immune Checkpoint Inhibitors in Sarcoma

Scandinavian Sarcoma Group

Introduction

Immune checkpoint inhibitors (ICIs) are drugs that block the interaction between immune checkpoint proteins. This will prevent inhibitory signaling in immune cells, thus resulting in stimulation of an antitumor immune response. The most commonly used ICIs are antibodies targeting the programmed death receptor-1 (PD-1) or its ligand (PD-L1). In several tumor types, treatment with ICIs has resulted in durable responses in a significant number of patients with unresectable locally advanced or metastatic disease. Prospective clinical studies and studies with off-label use in sarcoma have also been reported. Here, we briefly summarize the existing evidence in sarcoma and propose Scandinavian Sarcoma Group (SSG) recommendations on the use of ICIs.

Summary of published data

An open-label phase 2 study with single-agent pembrolizumab in soft tissue and bone sarcoma was reported in 2017[1]. Among 40 patients with soft tissue sarcoma (STS), seven had an objective response (18 %), including 4/10 with undifferentiated pleomorphic sarcoma (UPS), 2/10 with dedifferentiated liposarcoma (DDLPS) and 1/10 with synovial sarcoma. Two of the 40 patients with bone sarcoma had an objective response, including 1/22 patients with osteosarcoma and 1/5 with chondrosarcoma. The observed responses were generally durable. Based on the encouraging activity in UPS and DDLPS, these cohorts were expanded to a total of 40 patients each. Nine of 40 patients with UPS (23%) and four of 40 patients with DDLPS (10%) had an objective response[2].

Another phase 2 study investigated the activity of nivolumab alone or in combination with ipilimumab[3]. Forty-three patients received nivolumab and 42 patients received the combination. Eight responses were observed, two with nivolumab and six with nivolumab and ipilimumab. The histological subtypes among responders included leiomyosarcoma (LMS; n=3), UPS (n=2), alveolar soft part sarcoma (ASPS), myxofibrosarcoma (MFS) and angiosarcoma. The distribution among subtypes was different compared to the SARC028 trial[1], as only 11 patients (13%) had UPS and 29 (34%) had LMS.

The French sarcoma group conducted a phase 2 trial with pembrolizumab in combination with metronomic cyclophosphamide in four cohorts of STS: LMS, UPS, gastrointestinal stromal tumor (GIST) or other sarcomas[4]. Among 50 evaluable patients, only one partial response was observed in a patient with solitary fibrous tumor. Other trials combining ICIs with conventional or experimental agents have also been performed. A phase 2 study investigated the combination of pembrolizumab and the tyrosine kinase inhibitor axitinib[5]. Eight of 32 evaluable patients had a partial response (25%), of whom seven had ASPS. In a small, single-arm study with pembrolizumab and the oncolytic immunotherapy talimogene laherparepvec (T-VEC), seven of 20 patients (35%) had objective response[6]. Response was observed in five histological subtypes: cutaneous angiosarcoma (n = 2), UPS (n = 2), MFS, epithelioid sarcoma, and unclassified sarcoma. A trial combining pembrolizumab with

doxorubicin reported an overall response rate of 19% in 37 patients, including three patients with UPS and four with dedifferentiated liposarcoma[7]. It is, however, difficult to interpret response rates in this setting, as doxorubicin alone has significant antitumor activity. On the other hand, four patients had ongoing partial responses who had lasted >1 year at the time of data cut-off.

Preliminary data from a phase 2 study with single-agent atezolizumab in ASPS was reported at in 2018[8]. Eight of 19 patients had confirmed partial response, and all patients with response were still receiving treatment with treatment duration of at least 6 months.

In angiosarcoma, patients with cutaneous localization have high response rates to ICIs. It has been shown that angiosarcoma of the head, neck, face and scalp (HNFS) have a high tumor mutation burden and a dominant ultraviolet damage mutational signature, similar to malignant melanoma[9], indicating that ICIs could be of benefit. Indeed, two patients with HNFS angiosarcomas had durable responses to pembrolizumab[9], and four of five patients with cutaneous angiosarcoma had objective response in an institutional case series[10]. Recently, preliminary results from the angiosarcoma cohort of the DART study combining nivolumab and ipilimumab was presented[11]. Four of 16 patients had an objective response, including three of five patients with HNFS angiosarcoma.

In patients with classic/endemic type Kaposi sarcoma, a HHV 8 associated sarcoma subtype not related to known immune deficiency, emerging results on ICI based therapy with anti PD-1 alone or in combination with anti CTLA-4 are promising. Preliminary data from two phase 2 trials show objective clinical responses in 12 of 17 patients (71%) treated with pembrolizumab[12], and in 10 of 15 patients (66%) treated with nivolumab and ipilimumab[13]. Durable responses were reported in both trials and the toxicity profile is similar to published results from larger trials and real word setting in other cancer types.

Responses to ICIs have also been observed in ultra-rare sarcoma subtypes, including chordoma, desmoplastic small round cell tumor (DSCRT), malignant rhabdoid tumor, malignant peripheral nerve sheath tumor (MPNST) and epithelioid sarcoma[14-19].

Recommendations

There are no ICIs approved by EMA for use in any sarcoma subtype. All use of ICIs in sarcoma in Europe will thus be considered off-label. Reimbursement of off-label use in the public health care systems in the Nordic countries depends on local and national decisions, and might be different between hospitals, regions and countries. The present recommendations should be considered as a guideline if treatment with ICI is considered and is possible according to local and/or national regulations. Inclusion in clinical studies should be of high priority, if possible. We emphasize that individual considerations must also be taken into account, such as age of the patient, performance status and comorbidities. Since the recommendations are histology-specific, pathology review by a reference sarcoma pathologist should be conducted.

We recommend that the use of ICI beyond first line therapy may be considered in the following sarcoma subtypes and clinical settings:

1. UPS: monotherapy with PD-1 inhibitor in patients with unresectable, locally advanced or metastatic disease. No studies have addressed the scheduling of treatment, and no specific

recommendation with regard to which line of treatment is thus given. In the largest study that showed durable responses in 23% of patients, patients could have received up to three lines of prior systemic treatment.

2. ASPS: monotherapy with PD-1 or PD-L1 inhibitor or combination of PD-1 inhibitor and axitinib in patients with unresectable, locally advanced or metastatic disease. No studies have compared ICI alone compared to ICI plus axitinib. Both regimens have shown high response rates and durable responses.
3. Angiosarcoma - cutaneous: monotherapy with PD-1 inhibitor in patients with unresectable, locally advanced or metastatic disease.
4. Kaposi sarcoma - classic/endemic type: monotherapy with PD-1 inhibitor in patients with unresectable locally advanced or metastatic disease.
5. Selected, ultra-rare subtypes: monotherapy with PD-1 inhibitor in patients with unresectable, locally advanced or metastatic disease. Here, the data are scarce, and no firm recommendations are given. The response rates and durability of response must be considered for each subtype, and weighed against other available therapy.

There are several trials combining ICIs with conventional or experimental agents, and also combinations with ipilimumab and nivolumab. There are no studies conclusively demonstrating superiority of a combination regimen. On this basis, we have chosen to recommend monotherapy, since combination regimens in general are associated with more toxicity. The only exception is pembrolizumab and axitinib, which is considered equivalent to monotherapy in ASPS. However, combination strategies may be considered in selected cases based on individual considerations.

In general, we do not recommend treatment with ICI in common sarcoma subtypes that are not mentioned above. For histological subtypes such as LMS, MFS, osteosarcoma and Ewing sarcoma, only occasional responses have been observed, and we consider the response rates too low to recommend ICI treatment. For DDLPS, a response rate of 10% has been reported. It might be discussed whether this histology should be included in the recommendations. If ICI treatment is considered in patients with liposarcoma, even more emphasis should be put on patient factors such as age, performance status and comorbidities.

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