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SYSTEMIC THERAPY FOR CARDIAC SARCOMAS

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Introduction

Cardiac sarcomas create 2 risks: local problems and metastatic disease. Most frequently, the histologies are angiosarcoma and high-grade pleomorphic unclassified sarcoma (formerly called MFH or malignant fibrous histiocytoma). There is also a clinical-pathological entity without distinctive histological features of tumors that originate in the pulmonary artery and are referred to as pulmonary artery sarcomas or intimal sarcomas of the pulmonary artery. Conventional wisdom indicates that soft-tissue sarcomas are poorly responsive to chemotherapy. Luckily, that is not the case. Attempts to concentrate on the local problem only with therapies up to and including cardiac transplantation have been unsuccessful due to the high rate of fatal metastatic disease.

Cytotoxic Chemotherapy

There are 2 combinations of standard chemotherapeutic drugs that can be beneficial in treating cardiac sarcomas: Adriamycin (doxorubicin) and ifosfamide, and gemcitabine and docetaxel. Most of the histological types of sarcomas that originate in the heart can respond to either or both of these regimens. For angiosarcomas, there are additional options.

The key to effective use of Adriamycin and ifosfamide is dose intensity. For Adriamycin, a randomized dose-response study showed a doubling of response rate at a dose of 75 mg/m^2 compared with 45 mg/m^2.[1] For ifosfamide, the data are weaker, but our data indicate higher responses at higher doses.[2, 3] Based on this information, the standard Adriamycin-ifosfamide regimen at MD Anderson is Adriamycin at 75 mg/m^2 and ifosfamide at 10 g/m^2, and for younger, relatively healthy patients otherwise, we usually use Adriamycin at 90 mg/m^2.[4] Of course, we always use a granulocytic growth factor to minimize the period of severe neutropenia, and we always give the Adriamycin with a cardioprotective strategy, usually continuous infusion over 72 hours and less frequently by rapid infusion with dexrazoxane. When mucositis limits tolerance, the shorter infusion is somewhat protective. Alternatively, palifermin at 180 mcg/m^2 given 3 days prior to Adriamycin infusion is effective at minimizing the mucositis.[5] Ifosfamide is given in divided doses over 3 hours daily for 4 to 5 days, in conjunction with alkaline fluids and mesna. Ifosfamide is limited by nephrotoxicity and neurotoxicity. Nephrotoxicity is minimized by adequate hydration and, in some cases, by renal doses of dopamine. Neurotoxicity is minimized by assuring alkalinization (never let the CO_2 go below 26) and by higher levels of serum albumin; we administer albumin prior to ifosfamide for anyone who has a borderline albumin level, or when a prior course caused neurotoxicity. Fortunately, it is always reversible, so there is no need to stop therapy in the presence of neurotoxicity. About 60% of patients will have objective tumor shrinkage and an additional 20%–30% will have lesser shrinkage or stabilization of previously progressive disease.

The combination of gemcitabine and docetaxel has been demonstrated to have greater activity than gemcitabine alone in a study carried out by the Sarcoma Alliance for Research through Collaboration (SARC), designed as a phase III study for patients with progressive disease after standard chemotherapy. The study

was a Bayesian adaptively randomized study, and was ultimately published as a phase II study as an editorial decision by the journal.[6] Taxanes have no activity as single agents in most sarcomas, but they are highly active in angiosarcomas of the scalp and have some, but much less, activity in primary angiosarcomas of other primary sites. Gemcitabine has single-agent activity in sarcomas, so the gemcitabine-docetaxel combination is particularly attractive for angiosarcomas.[7, 8] The histological type most sensitive to the gemcitabine-docetaxel combination in the salvage setting was MFH, so this combination is also attractive for cardiac sarcomas.

One of the limiting side effects of this combination is fluid retention from the docetaxel, and when that occurs, we recommend continuation of gemcitabine with increased dose if tolerated. Gemcitabine requires phosphorylation to be incorporated into DNA, and the phosphorylation is limited to 10 mg/m^2/min, so the relatively rapid infusion of gemcitabine when used according to the package insert results in excretion of a substantial portion of inactivated drug.[8] For good-risk patients taking the gemcitabine-docetaxel combination, gemcitabine is given on days 1 and 8 at 900 mg/m^2 over 90 minutes and docetaxel at 100 mg/m^2 over 60 minutes. For poor-risk patients, gemcitabine is given at 675 mg/m^2 over 70 minutes and docetaxel at 75 mg/m^2 over 60 minutes.

Targeted Therapy of Cardiac Angiosarcomas

Since angiosarcomas are malignant tumors with functional and morphological features of normal endothelium, targeted agents that inhibit the process of new blood vessel growth have been a source of great interest in the treatment of these tumors. Angiogenesis, the process of endothelial proliferation and formation of microvessel sprouts, is physiologically brought about by the interaction of a host of angiogenic factors and inhibitors. Pathological angiogenesis, seen in tumors and some other diseases, continue to depend on tipping the balance of these factors in favor of new blood vessel formation. With the aid of drugs that inhibit angiogenesis, we hope that malignant proliferating endothelial cells can be inhibited and thereby arrest the growth of these tumors.

Cardiac angiosarcomas are extremely rare, and large studies examining the utility of targeted agents in treating these are unavailable. Most of the data comes from small trials that enroll a variety of sarcomas, including angiosarcomas. Agents that inhibit angiogenesis may have a role in the treatment of angiosarcomas, and may be broadly classified into 3 groups depending on the number of angiogenic proteins they inhibit. It is important to make the distinction between agents that inhibit only a single angiogenic protein from others that affect multiple target proteins, as it may be relevant to the efficacy of these agents and to the development of drug resistance. Most tumors can express multiple angiogenic proteins[9] and tend to develop drug resistance more readily when treated with agents with activity towards 1 specific target. Another critical aspect to consider while choosing therapy is the rate of progression of cardiac angiosarcomas. It should be borne in mind that monotherapy with anti-angiogenic agents works best in slow-growing tumors, and is best avoided in rapidly progressive tumors. Cytotoxic chemotherapy, either alone or in combination with targeted agents, should be considered in those situations.

Group I: Drugs that Inhibit 1 Main Angiogenic Protein

Bevacizumab (Genentech, South San Francisco, California) is a humanized monoclonal anti-vascular endothelial growth factor (anti-VEGF) antibody that is currently widely used in the treatment of colorectal, lung and breast cancers in combination with cytotoxic chemotherapy. The agent appears to have limited activity as monotherapy, and the same is true for angiosarcomas. Combination therapy of bevacizumab with doxorubicin was examined in a phase II trial that enrolled 17 patients with sarcoma; unfortunately, no angiosarcomas were enrolled. This trial raised some toxicity concerns as a grade 2 decline in LVEF was observed in one-third of the patients. Cardiac toxicity was often reversible — of the 6 patients who had a decline in cardiac ejection fraction, 5 showed improvement over time.[10] Since doxorubicin appears to have good activity in cardiac angiosarcomas, the role of the combination needs further study. Combination of gemcitabine and docetaxel with bevacizumab has been shown to have activity in angiosarcoma, and the authors reported 2 complete responses in patients with angiosarcoma.[18] The role of bevacizumab in these responses is unknown since the chemotherapy combination is definitely active by itself, in our experience. Currently, there are 3 trials that are recruiting patients looking at the efficacy of bevacizumab in the treatment of angiosarcomas: the first is a monotherapy trial, the second is a combination of gemcitabine and docetaxel with or without bevacizumab, and the third is a combination of paclitaxel and bevacizumab. These trials are specific for angiosarcoma, and will have sufficient numbers of patients with angiosarcoma enrolled in them to derive useful conclusions about the utility of this agent in angiosarcoma therapy.

Group II: Drugs that Inhibit 2 or 3 Main Angiogenic Proteins

Sunitinib (Sutent, Pfizer Inc., New York, NY) is a multi-targeted tyrosine kinase inhibitor with activity against multiple targets, including VEGF-R2, platelet-derived growth factor (PDGF) receptor and c-KIT receptor. It also has activity against Flt-3, neurotrophic factor receptor and CSF-1, and blocks VEGF receptors 1 through 3.[11] Data on the utility of this agent in treating angiosarcomas is limited, as the only published study on the activity of this agent in non-GIST (gastrointestinal stromal tumor) sarcomas enrolled 2 patients with angiosarcoma, and both patients failed to show a response.[12]

Sorafenib (Nexavar, Onyx, Emeryville, California, and Bayer, Leverkusen, Germany) is a multi-targeted tyrosine kinase inhibitor with activity against Raf, PDGFR, VEGF-R2, VEGF-R3 and c-KIT. The activity of this agent was examined in a phase II trial that enrolled 37 patients with angiosarcoma, and 5 patients (14%) showed a response to sorafenib. The only patient to develop a complete response to treatment was an angiosarcoma patient; 4 other patients had a partial response.[13] In another trial that enrolled 37 patients with sarcoma, 7 out of 9 patients with vascular tumors had stable disease with a median progression-free survival of 4.7 months.[19] Clinical trials examining the combination of sorafenib with cytotoxic agents such as dacarbazine are currently underway.

Group III: Drugs that Block a Wide Range of Angiogenic Proteins

This group includes agents that have a broad spectrum of activity against a wide range of angiogenic regulators. Examples include endostatin and caplostatin that downregulate VEGF, bFGF, bFGF receptor, HIF1α, EGF receptor, ID1 and neuropilin, and upregulate thrombospondin. Currently, there are no published data evaluating the role of these agents in cardiac angiosarcomas, but it is an area requiring investigation.

Key Concepts for Effective Inhibition of Angiogenesis in Tumors

While cytotoxic chemotherapy is intended to cause tumor cell death by a direct effect, anti-angiogenic therapy can exert its effect on endothelial proliferation either directly (by inhibiting the endothelial cells) or indirectly (by reducing the tumor's production of angiogenic proteins). There are several differences between the cytotoxic strategy and the anti-angiogenic strategy that need to be considered while picking a treatment for particular clinical situation.

Tumor growth rate. Angiosarcomas can grow quite rapidly, and the rate of progression of the tumor needs to be considered while developing a therapeutic strategy. Cytotoxic chemotherapy is more effective on rapidly growing tumors, while anti-angiogenic therapy works best in slow-growing tumors.[9] Consequently, monotherapy of rapidly growing angiosarcomas with anti-angiogenic agents may not be effective. In such situations, a cytotoxic agent alone or in combination with an anti-angiogenic agent may be a better choice. After several cycles of chemotherapy as the disease settles to a stable status, monotherapy with anti-angiogenic agents may be considered with close radiological monitoring.

Relationship between dose and response. Dose and response tend to have a more linear relationship with cytotoxic chemotherapy. Anti-angiogenic agents tend to have a biphasic, U-shaped dose efficacy curve, where blood levels that are too low or too high may be ineffective in the inhibition of angiogenesis. This biphasic dose efficacy of anti-angiogenic agents needs to be considered while using these drugs alone and in combination with cytotoxic chemotherapy. More is not necessarily better when it comes to anti-angiogenesis, and this has been demonstrated in interferon-α[14] and endostatin.[15]

Frequency of dosing. Cytotoxic chemotherapy is often administered at the maximum tolerated dose with a long off-therapy interval to allow for bone marrow and mucosal recovery. While this might be optimal for producing cytotoxicity, anti-angiogenic therapy requires endothelial cell exposure to steady blood levels of the inhibitor.[16] Hence, anti-angiogenic agents with a short half-life need to be dosed daily and without any breaks.[9]

Adverse effects. Side effects of anti-angiogenic therapy are different from those of cytotoxic agents. Unlike cytotoxic agents, myelosuppression, nausea and hair loss are all unusual with anti-angiogenic therapy, while a whole host of other side effects such as hypertension, bleeding, bowel perforation and thromboembolism can occur. Evaluation of the side-effect profile against the backdrop of the patient's existing medical problems is an important step while choosing therapy. Combination of cytotoxic therapy with anti-angiogenic therapy may increase the risk of thromboembolism over monotherapy.[17]

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