Multimodality therapy for metastatic sarcomas confined to the lung (Review)

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Abstract. Metastectomy or resection of sarcomas which have metastasized to the lung from other sites has a long and established history. At present, there are more than forty different drugs with activity in soft tissue sarcomas. A number of sarcomas demonstrate differential sensitivities to chemotherapy and targeted agents. Intimate knowledge of the biological behavior of each distinct type of sarcoma should predicate what treatment or protocol is most suitable. Certain patients might benefit from either neoadjuvant or adjuvant therapy following the resection of metastatic lesions. Much remains to be learned about the differential sensitivities of various sarcomas to different treatment regimens.

Contents

1. Multimodality therapy for pulmonary soft tissue sarcomas

Sarcomas of the lung present a difficult problem. They are uncommon, and it should first be determined if they are primary or secondary to sarcomas in other parts of the body. The multiplicity of different types of sarcomas, both soft tissue and bone/cartilage, a number of which demand therapy tailored to the specific cell type and grade, make it incumbent for the treating oncologist, pulmonologist and surgeon to have an intimate knowledge of the differential treatment regimens and protocols for this group of similar yet distinct tumors. It must first be determined whether the tumors are primary to the lung or the result of metastases from elsewhere in the body. Metastectomy has a long history in the management of multiple tumors from other sites that have spread to the lungs, particularly late recurrences from primary sarcomas extirpated from other parts of the body. The natural history of metastatic sarcomas in the lung is terminal (1-3). Colorectal adenocarcinomas, which are far more common than sarcomas, commonly spread to the lungs and are often resected and chemotherapy is administered neoadjuvantly or adjuvantly. These resections may be completed for cure.

Even amongst extremely rare sarcomas encountered in the lung, resections may occasionally be completed for cure in lesions sensitive to treatment if the differential sensitivity to both cytotoxic and targeted therapy is considered and the tumors are treated with these differential sensitivities in mind. Adult sarcomas are rare both individually and collectively. With approximately 12,000 cases reported in the United States every year, even the more 'common' types of sarcomas are found in relatively small numbers (American Cancer Society website; www.cancer.org). Malignant fibrous histiocytomas, liposarcomas and leiomyosarcomas are the most common soft tissue sarcomas encountered in adults. Generally, extremity sarcomas have a better prognosis than truncal sarcomas. When a non-calcified soft tissue mass is found within the thorax, a core needle biopsy should be used to determine the histology of the lung lesion. A thorough physical examination, including a gynecological examination for females, should be completed prior to obtaining expensive imaging.

Similar to lymphomas, sarcomas are derived from the mesoderm and a number are characterized by fusion translocations (Table I) (4). Oncogenesis is complex and may be a step-wise process which is initiated by inactivation of the p53 pathway. Probes against transfusion translocations (fluorescence *in situ* hybridization, FISH, and silver *in situ* hybridization, SISH) may be used for tumor identification when histological analysis, immunohistochemistry and other pathological investigations are not fully or definitively diagnostic. Other sarcomas are characterized by complex karyotypes lacking specific activating translocations.

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Table I. Chromosomal translocations in sarcomas.

Histological subtype	Translocation	Gene fusion
Synovial sarcoma	t(X;18)(p11.2; q11.2)	*SYT-SSX1* *SYT-SSX2* *SYT-SSX4*
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*FUS-CHOP*
	t(12;22)(q13;q11)	*EWS-CHOP*
Alveolar rhabdomyosarcoma	t(2:13)(q35;q14)	*EWS-ATF1*
	t(1:13)(p36;q14)	*PAX3-FKHR*
Alveolar soft part sarcoma	t(X;17)(p11;q25)	*PAX7-FKHR*
Desmoplastic round cell tumor	t(11;22)(p13;q12)	*EWS-WT1*
Epithelioid hemangioendothelioma	t(1;3)(p36.3;q25)	Unknown
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22-q3;q12)	*EWS-NR4A3*
	t(9;17)(q22:q11)	*TAF15-NR4A3*
Ewing Sarcoma	t(11;22)(q24;q12)	*EWS-FLI1*

Adapted from ref (4).

2. Imaging modalities

Usually a CAT scan of the chest is performed when a mass lesion is first identified; this is often followed by a PET scan and CAT scan of the abdomen and pelvis and a bone scan as well as an MRI of the brain to complete imaging. In sarcomas, MRI scans are usually ordered, particularly with mesotheliomas, due to the ability to identify layers of fascia and discern levels of invasion within layers of muscle, fat and connective tissue on T1 and T2 images enhanced with gadolinium contrast. Sarcomas of the bone and cartilage, particularly those located in the extremities, are staged with MRI of the affected limb and CAT scans of the chest, abdomen and pelvis.

PET scans have been shown to be useful in the staging of certain sarcomas. Currently Medicare only allows for PET scans in patients with solitary pulmonary nodules and for the staging of more common tumors, including colon cancers, non-small cell lung cancers, melanomas and lymphomas.

3. Surgical approaches and techniques

Before making an attempt at surgical resection, different modes of resection must be considered, including thoracotomy followed by pneumonectomy, wedge resection or lobectomy. Less severe surgery is favored due to the occasional bilateral nature of metastatic disease and the occasional need for resections at different times. More extensive surgery, however, is favored as part of trimodality therapy (chemotherapy, surgery, radiation therapy) in individuals with mesothelioma. Thoracoscopy, bronchoscopy and mediastinoscopy have important roles. Due to the importance of directly visualizing both the parietal and visceral pleura for subtle evidence of metastatic involvement, less invasive modalities than thoracotomy may occasionally be used to determine resectability. Thoracotomy unfortunately remains the mainstay of metastectomy due to the wide exposure a traditional thoracotomy incision confers. As in non-small cell lung cancer, direct visual inspection of the chest cavity may lead to immediate surgical upstaging of a tumor and may occasionally necessitate that curative surgery either be aborted or deferred to another time. Surgical treatment of pulmonary metastases changes the natural history of the disease (5-18).

Video-assisted thoracic surgery (VATS; previously referred to as pleuroscopy) is a less invasive form of thoracic surgery which has become increasingly popular over the last 20 years. A trained thoracic surgeon uses a video camera attached to a modified endoscope to inspect the pleura and perform diagnostic and therapeutic procedures. The introduction of stapling through the thoracoscope has enabled thoracic surgeons to perform surgical procedures through the VATS procedure that would previously have been performed through an open thoracotomy. Specifically, lobectomy and wedge resections may be performed through VATS procedures without the prolonged healing time associated the more traditional thoracotomy. VATS lobectomies are similar to open lobectomies in that the pulmonary anatomy remains the same; branches of the pulmonary arteries and veins, as well as the bronchus to the involved lobe, must be divided and ligated prior to resection. Whether VATS may become a mainstay in metastectomy is questionable due to the scarring surrounding certain metastatic lesions following exposure to neoadjuvant treatment. Extensive reconstruction of vascular structures, which is commonly carried out in extremity sarcomas, is generally not performed with central vasculature when resecting pulmonary sarcomas (19-23).

When there is a question of mediastinal involvement, direct inspection of the anterior mediastinum, which allows inspection and sampling of level 2, 4 and 7 lymph nodes, should be performed. A traditional mediastinoscopy starts with an incision at the sternum, through which an extended mediastinoscopy may be carried out and lymph nodes in the preaortic position and aorto-pulmonary window (levels 6 and 5) may be

sampled. The Chamberlain procedure, or paramedian mediastinotomy, which involves entering the mediastinum below the sternal notch from between the third and fourth ribs, is the standard procedure for obtaining lymph nodes from levels 5 and 6.

4. Radiation therapy

Radiation therapy is not often used in the treatment of sarcomas of the chest, except in a palliative role. Sarcomas are generally not sensitive to radiation; normal lung tissue may be killed at a dose of more than 2,000 cGy, whereas sarcomas require 6,000 to 10,000 cGy for eradication. Cyber-knife therapy may have a role for single metastatic lesions but cannot be used for large or multiple lesions. Similarly, adjuvant radiation, useful in extremity sarcomas, is not generally useful in lung sarcomas (24-28).

5. Chemotherapy and targeted therapy

Unlike lymphomas, which are also derived from the mesoderm, sarcomas are not generally curable with chemotherapy. Most studies of chemotherapy efficacy mix these tumors due to the rarity of individual multiple histologies, except perhaps for mesotheliomas. Starting in the 1970s, several different schools of thought predominated on the treatment of soft tissue sarcomas. Arterial infusions of Adriamycin were used for extremity sarcoma (29). Cisplatin-based multi-agent protocols were utilized at the Mayo clinic, while multi-agent regimens containing ifosfamide, mesna, dacarbazine and Adriamycin were developed at Memorial Sloan Kettering and Dana Farber (30). High-dose methotrexate, with Adriamycin and ifosfamide, was found to be an active combination in osteosarcomas (31). Before a great variety of drugs was available, much time was spent developing novel regimens that could be administered as prolonged infusions over 24 h to one week or over a short period of time to achieve a high peak plasma concentration. Numerous other agents, including dacarbazine, doxorubicin and ifosfamide, were developed using different treatment schedules (32-38). Gemcitabine and Taxotere were found to act synergistically in metastatic leiomyosarcomas (39). The differential sensitivity of certain sarcomas to other agents, including angiosarcomas to taxanes and mixed mullerian tumors, particularly high grade carcinosarcomas, to ifosfamide and cisplatin, further muddies the water regarding differential sensitivity to various agents. With the advent of Gleevec, the prototypal targeted therapy for select sarcomas, it is possible to use other targeted agents with targeted therapy (40). Even with some low-grade or borderline malignant tumors previously thought to be insensitive to chemotherapy, there are now data that indicate that chemotherapy has a role, as in desmoid tumors (41-43). This landscape is further complicated by data which have been confusing with regard to the long-term benefit of adjuvant chemotherapy in limited stage soft tissue sarcomas (44-47). The treatment choices may now be molecularly driven with our increasing knowledge of translocations and gene fusion products (48-51).

A number of the studies on extremity sarcomas have been directed toward reducing the size of extremity sarcomas, such that limb-sparing surgery may be performed. The same approach may be utilized in patients with lung metastases from primary sarcomas. Treatment should be tailored as much as possible to the subtype. As medical knowledge further characterizes these translocations and the oncogenes that may be amplified as a result, more targeted agents are likely to become available. Knowledge of these translocations is paramount in making appropriate diagnoses as numerous probes have become commercially available that are able to identify, by FISH, the presence of certain diagnostic mutations.

Exact diagnoses are paramount, as different types of sarcomas require different types of systemic treatment. Low-grade sarcomas have been thought to be insensitive to chemotherapy, though this is not always the case. Intermediate- and high-grade sarcomas exhibit differential sensitivity to cytotoxic agents. The location of tumors may be predictive of responses, but histology is more accurate. Pediatric sarcomas present special cases; in particular, Ewing sarcoma, the Ewing sarcoma family of tumors and osteosarcomas require specialized treatment protocols developed for the pediatric population. Targeted therapy has value in gastrointestinal stromal tumors (GISTs). The relative rarity of individual subtypes belies their importance in illustrating the importance of tailoring therapy to specific histology, biology and location. The development of specialized target therapies has allowed progression beyond the inaccurate treatment paradigms which have become outdated in the past 10 years, and which mandated that all intermediate- and high-grade lesions be treated with combinations of doxorubicin, ifosfamide and dacarbazine or not at all, and that low-grade sarcomas need not be treated at all, except by the surgeon and radiotherapist, due to their supposed insensitivity to drug therapy. Despite the more aggressive nature of intermediate- and high-grade lesions, they respond at a higher rate to chemotherapy than do low-grade regimens.

The relative insensitivity of low-grade sarcomas to chemotherapy should not suggest that they are insensitive to all forms of therapy; rather it indicates the need for subtyping individual sarcomas and for immunohistochemical phenotyping and molecular genotyping.

It is known that differential drug sensitivities exist in sarcomas. Doxil and taxanes are recommended for angiosarcomas previously considered to be insensitive to chemotherapy (52). Sunitimab is recommended for alveolar soft tissue sarcoma (53). Combinations of Adriamycin, ifosfamide and methotrexate remain the mainstay of treatment for osteosarcomas. Rhabdomyosarcomas are best treated with vincristine, Adriamycin and Cytoxan in combination. Gemcitabine and Taxotere are particularly effective in GI leiomysarcomas and myxoid round cell tumors are particularly sensitive to trabectedin (54). Synovial sarcomas also appear to be sensitive to trabectedin as well as to traditional regimens which contain Adriamycin and ifosfamide and Nexavar, as do small round cell tumors (55-58). Chondrosarcomas remain amongst the tumors which are insensitive to chemotherapy, particularly the grade I sarcomas whereas the grades II and III sarcomas, particularly the mesenchymal subtype, do have some sensitivity to Adriamycin- and ifosfamide-based regimens (59). Epithelioid sarcomas are also known for tumor resistant behavior amongst soft tissue sarcomas (60).

Sirolimus appears to have activity in perivascular epithelial cell tumors (recurrent angiomyolipoma/lymphangioleiomyo-

matosis) (61-64). With the advent of molecular genotyping and phenotyping, these and other sensitivites may be prospectively studied and predicted (65). Further development should focus on less toxic agents, including VEGF inhibitors, tyrosine kinase inhibitors, PDGFR inhibitors, EGFR inhibitors and agents with novel mechanisms of action (66,67). mTOR inhibitors have been studied in the metastatic sarcoma subpopulation. Ridaforolimus, a rapamycin analog, has been studied in sarcomas and may confer stability of disease while not having the adverse toxicities of combination chemotherapy (68-71). The SUCCEED trial has studied this drug at multiple centers (72).

The histogenesis of soft tissue sarcomas may point to the efficacy of therapy that targets signal transduction. Soft tissue sarcomas are thought to be derived from primitive mesenchymal cells which are found throughout the body, not just in mesodermal derivatives such as supportive tissue and muscle. Common pathways may be dysregulated when activated in different sarcoma subtypes.

Most practicing oncologists are familiar with routine rejections for off-label uses of newer, more expensive chemotherapies and targeted therapies. Unfortunately, the relative rarity of sarcomas ensures that large randomized protocols are unlikely to occur for most newer targeted therapies. Rather, evidence may consist of pooled data, small studies, cooperative groups, phase II studies and case reports. Since level I data do not exist, oncologists may find themselves as unwitting activists for access to tailored therapies. As many sarcomas occur in the younger population, physicians may be called on to advocate for access to expensive drugs that, over the long-term, may provide disease stability (73-76). Considering individual sarcomas as 'orphan diseases' so that proper and efficacious medicines may be developed and offered for treatment may be a solution; advocacy for other relatively rare disease, including Gaucher's disease and hemophilia A and B, has resulted in numerous effective therapies along with long-term disease management with decreasing morbidity and mortality. The costs of such therapies are insignificant when compared with the human costs of no, toxic or ineffective therapies.

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