Published OnlineFirst May 6, 2014; DOI: 10.1158/1078-0432.CCR-13-2574

Clinical Cancer Research

Perspectives

Toward a Drug Development Path That Targets Metastatic Progression in Osteosarcoma

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Abstract

Despite successful primary tumor treatment, the development of pulmonary metastasis continues to be the most common cause of mortality in patients with osteosarcoma. A conventional drug development path requiring drugs to induce regression of established lesions has not led to improvements for patients with osteosarcoma in more than 30 years. On the basis of our growing understanding of metastasis biology, it is now reasonable and essential that we focus on developing therapeutics that target metastatic progression. To advance this agenda, a meeting of key opinion leaders and experts in the metastasis and osteosarcoma communities was convened in Bethesda, Maryland. The goal of this meeting was to provide a "Perspective" that would establish a preclinical translational path that could support the early evaluation of potential therapeutic agents that uniquely target the metastatic phenotype. Although focused on osteosarcoma, the need for this perspective is shared among many cancer types. The consensus achieved from the meeting included the following: the biology of metastatic progression is associated with metastasis-specific targets/processes that may not influence grossly detectable lesions; targeting of metastasis-specific processes is feasible; rigorous preclinical data are needed to support translation of metastasis-specific agents into human trials where regression of measurable disease is not an expected outcome; preclinical data should include an understanding of mechanism of action, validation of pharmacodynamic markers of effective exposure and response, the use of several murine models of effectiveness, and where feasible the inclusion of the dog with naturally occurring osteosarcoma to define the activity of new drugs in the micrometastatic disease setting. *Clin Cancer Res; 20(16); 4200–9. ©2014 AACR.*

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doi: 10.1158/1078-0432.CCR-13-2574

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Published OnlineFirst May 6, 2014; DOI: 10.1158/1078-0432.CCR-13-2574

Translational Relevance

A focus on drug development that targets metastatic progression and not necessarily regression of measurable lesions is needed to improve the stagnant long-term outcomes for patients with osteosarcoma. Through the input of key opinion leaders in the fields of metastases biology and osteosarcoma, the following "Perspective" represents a consensus on the relative value and priorities of a preclinical dataset that would support the translation of a novel therapeutic toward clinical development in patients with osteosarcoma. Such a metastasis-focused and rigorous preclinical dataset is needed for such translation as we may not be able to rely on early human clinical trials of tumor regression to support the development of these potentially valuable therapeutic agents.

Introduction

As is the case for many solid tumors, the problem of metastasis is the most important cause of morbidity and mortality in patients with osteosarcoma. On the basis of historical data, more than 80% of patients will progress to develop metastasis following resection of the primary tumor alone, and even with the addition of chemotherapy to primary tumor resection, approximately one third of the patients presenting with localized disease will subsequently develop pulmonary metastases (1, 2). Long-term outcomes for patients with osteosarcoma with either localized or metastatic disease have not substantively improved in more than 30 years; however, progress in our understanding of metastasis biology now offers hope to address this unmet clinical need. Recent studies have defined the existence of druggable targets linked to metastatic progression of cancer (3–7). Many of these targets and associated processes seem to specifically influence the progression of metastatic cells from microscopic disease to that of grossly detectable lesions (8). The modulation of these targets using either genetic or pharmacologic approaches may have no measurable effect on established and grossly detectable lesions at either the primary or metastatic locations (9, 10). As such, these agents are predicted to fail in conventional early-phase human trials that require regression of established disease (8, 11). Preclinical therapeutic studies in a variety of cancer histologies now support this prediction; novel therapeutic agents designed from an understanding of the unique vulnerabilities and targets linked to metastatic progression are indeed active against metastatic progression but may have no activity in the setting of measurable disease (12–14). In order for novel agents that target metastatic progression to advance, clinical trials conducted in the adjuvant setting, in the absence of measurable disease, will be required early in the drug development path. As noted above, our past reliance and requirement for regression of measurable lesions to advance therapeutic agents in drug development for osteosarcoma has not been rewarding. Accordingly, rigorous preclinical data will be necessary to support the evaluation of a drug whose activity and therapeutic benefit may be limited to preventing progression of existent microscopic disease, without the expectation of measurable anticancer activity in conventional response-based clinical trials. To advance the development of such novel therapeutics, a meeting of key opinion leaders and experts in the fields of bone sarcoma biology, metastasis, preclinical cancer drug development (including cancer biologists and veterinary oncologists), and the clinical management of patients with osteosarcoma (pediatric oncologists, medical oncologists, radiation oncologists, and surgeons) was convened in Bethesda, Maryland on April 6, 2013, with the support of the QuadW Foundation, the Children's Oncology Group, and CureSearch. The goal of this meeting was to establish a consensus "Perspective" on osteosarcoma drug development, which would focus on the problem of metastasis and establish a consistent translational path that could support the early evaluation of potential therapeutic agents that uniquely target the metastatic phenotype.

Osteosarcoma Drug Development Infrastructure

With the overriding goal of improving long-term outcomes for patients, the osteosarcoma community has initiated or participated in programs that can now support the development and integration of novel agents into osteosarcoma therapy. First, through the efforts of the QuadW–Children's Oncology Group Childhood Sarcoma Biostatistics and Annotation Office (CSBAO), a robust and clinically annotated osteosarcoma biospecimen repository is now available to fuel biologic investigations (J. Glover Personal Communication; ASCO 2013 Abstract). This repository has been linked to a relational database that will be progressively annotated with biologic analyses performed on these tissues, thereby allowing for the first time *in silico* analysis in this disease. Second, the NCI TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative is expected to deliver a greater understanding of osteosarcoma genomic targets that may be matched with existing or novel cancer therapeutics (http://ocg.cancer.gov/programs/target). Third, the Pediatric Preclinical Testing Program (PPTP) has an established infrastructure to test novel agents for their activity against primary tumor growth in a diverse set of osteosarcoma xenograft models (http://pptp.nchresearch.org/; ref. 15). Finally, the NCI Comparative Oncology Program has established a preclinical and translational consortium (COTC) that can rapidly evaluate the therapeutic value of novel agents in pet dogs that have naturally developed cancers most notably including osteosarcoma (https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home; ref. 16). With progress on these fronts, it is now feasible to integrate advances in our understanding of osteosarcoma and metastasis biology with preclinical and translational studies as a means to prioritize agents for evaluation in patients. It is recognized that for the successful implementation of this integrative approach, several existing drug development approaches, perspectives, and resources will need to be refocused on the

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problem of metastatic progression rather than regression of measurable cancer lesions alone.

The Quagmire for Osteosarcoma Metastasis Drug Development

The process of metastasis in patients with osteosarcoma seems similar to patients with other solid tumors. The steps associated with the metastatic spread of cancer cells from a primary tumor to a distant secondary site involve a complex set of discrete processes that are in many ways distinct from those associated with primary tumor growth (17–23). Most of the metastasis biology studies suggest that cancer cells readily gain entry to the circulation from the primary tumor, and that the majority of circulating cancer cells successfully arrive and extravasate at the distant secondary site; however, only a small minority of cells are able to survive at the distant and foreign microenvironment. Indeed, managing this critical stage of vulnerability is a defining feature of metastatic cells (24). Through a combination of selective and acquired events involving both genetic and epigenetic processes, metastatic cells are distinguished from nonmetastatic cells and are able to accommodate and adapt to the stresses incurred during metastatic progression (25). In some cases, the same oncogenic events linked to primary tumor formation and maintenance are also responsible for facets of the metastatic cascade, whereas other events are likely more intrinsically linked to the unique features of metastatic biology provided by metastasis-specific genes and gene regulation (26, 27). As such, there are unique targets and processes (often druggable) that may drive the progression of existent microscopic metastatic cells to grossly detectable lesions.

There are now sufficient experimental data to believe that the progression of single metastatic cells to established lesions occurs after patients present with apparently localized disease and continues after the development of radiographically detectable lesions. First, it is likely that those cells that are able to complete the steps of the metastatic cascade will subsequently metastasize to other parts of the same secondary organ or to distinct secondary sites late in clinical presentation (20, 28, 29). Second, it is reasonable that tumor cells remain dormant as quiescent single cells for long periods of time before they establish colonies of micrometastases in which a balance of proliferation and apoptosis exists, and before they progress to detectable lesions (19, 30, 31). Finally, it remains unclear whether this period of metastatic dormancy occurs at the secondary site (i.e., in the lung in the case of osteosarcoma) or in a so-called sanctuary sites (i.e., the bone marrow) with subsequent and therefore late spread to the eventual clinical secondary site (32–35). Accordingly, it is reasonable that targeting metastatic progression, particularly at the secondary site will provide clinical benefit to patients in all stages of presentation (i.e., it is not too late to target the metastatic cascade even after a patient develops metastasis).

Recognizing the imperative to assess new therapeutic agents that target the metastatic phenotype, a consensus on the nature of preclinical data needed to advance the clinical development of an antimetastatic agent is necessary. As this necessary translation is planned, it is important to recognize that decisions to advance a therapeutic agent to clinical development in the adjuvant-setting may need to be made without any prior evidence of antitumor activity in human patients. As outlined above, using input from experts in the field, we now propose a consensus "Perspective" toward this preclinical to clinical translational drug development challenge (Table 1). An important outcome of having a consensus on the types of data that are determined to be valuable, as a novel agent is proposed for translation, is that preclinical investigators will have a clear sense of what may be expected and similarly that translational groups will be clear on what they may expect as they evaluate and review therapeutic agents for potential clinical development. In addition to providing a clear consensus on the types of data that may be useful for translation of agents that target metastasis, Table 1 also provides a mechanism to compare or prioritize agents based on these data. Importantly, Table 1 is not intended to prescribe "go" or "no go" decisions on the suitability of potential agents, but rather serves to provide a consistent framework to objectively value and ascribe quantifiable merit to a list of novel agents being considered for translational assessment. In Table 1, vertical columns represent discrete translational data types that may be available for consideration in the preclinical to clinical translation of a novel therapy that targets metastasis. Within each column, a progressive merit score (PM Score) is assigned an integer value between 1 and 6, commensurate with the potential "value" of the data in that category. Similarly across columns, a relative merit score (RM Score) across data types is assigned an integer value between 1 and 3, and commensurate with our perceived "value" of that data-type to this drug development question. Using the PM Score (within a data type) and the RM Score (across data types), their product (PM Score $\times$ RM Score) is used to generate a cumulative relative dataset merit score, which then can be assigned and compared among distinct datasets for a specific translational therapeutic opportunity. The guidance provided in Table 1 will provide a collective understanding of the necessary and optimal dataset needed to advance therapeutic agents with activity against the metastatic phenotype and in-so-doing, will help prioritize those agents for clinical development in patients with osteosarcoma.

As outlined above, the pattern of failure for patients with osteosarcoma continues to involve the predictable development of metastasis to the lungs despite effective and complete control of the primary tumor. Despite attempts to intensify therapy, there has been a failure to decrease the development of metastasis and improve patient survival over the past 30 years. As such, there are no recent "historical controls" that can be used as positive "controls" to assess the scoring system. Accordingly, validation of the proposed approach will require prospective studies of novel therapeutic agents that are first evaluated through the proposed scoring system, which then move on to human clinical

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Table 1. Assessment of dataset supporting the preclinical to clinical translation of a novel therapeutic targeting osteosarcoma metastasis

	Translational data types[a]							
	Osteosarcoma target/ process biology and expression	**Drug mechanism of action and pharmacodynamics**	**Target modulation (pharmacodynamics)**	**Murine models**	**Canine osteosarcoma models**	**Pharmacokinetics**	**Human clinical data**	**PM Score within a data type[b]**
	Expression in cancer cell lines; not necessarily osteosarcoma	Drug and target biology linked to metastatic phenotype, demonstrated in multiple *in vitro* models		Evaluation of activity against primary tumor progression (agent may or may not have activity in this setting)	Target expression or biology understood and similar to human disease	Exposures believed to be active in model systems are achievable in patients	Complete phase I study that includes relevant exposure duration (does not need to be pediatric)	**1**
	Expressed at the protein level in osteosarcoma			Demonstration of significant activity against experimental (tail vein) metastasis for any cancer histology		Optimal dose and schedule in relevant patient population has demonstrated	Safety of new agent demonstrated in combination with MAP (or similar) chemotherapy	**2**
	Target or process expressed or active in reasonable proportion of patients with osteosarcoma			Demonstration of significant activity against one orthotopic spontaneous metastasis model of any cancer histology	In dogs with micrometastatic disease, demonstration of single-agent activity >8 months, or >24 months in combination with cytotoxic chemotherapy			**3**
	Expressed in osteosarcoma micrometastasis	Activity of agent demonstrated in complex models more reflective of metastasis (i.e., (PuMA)[d] or renal capsule invasion assay)	Target modulation demonstrated in relevant tissues/cells at achievable exposures	For immunologically based agents: evaluation in more than one syngeneic or GEM model of any cancer histology		PK, dose, and schedule in combination with chemotherapy similar to MAP has been demonstrated		**4**
	Target or process is abundantly present or active in metastatic osteosarcoma samples	Clear biologic rationale for activity specific for osteosarcoma	Target modulation linked to mechanism of action	Demonstration of significant activity against more than one orthotopic spontaneous, syngeneic, or GEM metastasis model (including at least one osteosarcoma model)				
		Activity against metastasis demonstrated in multiple *in vitro* models[e]	Target modulation in surrogate tissue appropriate for translation and therapeutic monitoring	Evaluation against metastatic progression in models derived from patients with chemoresistant or metastatic osteosarcoma	Demonstration of >50% improvement in EFS in dogs with micrometastatic osteosarcoma in a randomized placebo-controlled study design		Clinical activity against micrometastatic progression demonstrated in any human cancer or clinical activity against osteosarcoma	**6**
Relative merit across data types[c]	**1**	**1**	**2**	**2**	**3**	**1**	**3**	Cumulative relative dataset merit = relative merit × data type merit[f]

Abbreviations: MAP, methotrexate, doxorubicin, and cisplatin; PK, pharmacokinetics; GEM, genetically-engineered mice.
[a]Translational data type describes various types of data that will be collectively considered in the preclinical to clinical translation of a novel therapy that targets osteosarcoma metastasis.
[b]Progressive merit within a data type: scores from 1 to 6 will be applied to "value" the types of data provided within each data type. For example, under the data type of "Osteosarcoma Target Biology/Expression," the "expression of [a target] in cancer cell lines" is not viewed to be as valuable (PM Score of 1), compared with the "Target is abundantly present in osteosarcoma samples, or drug target is fundamental in osteosarcoma pathogenesis" (PM Score of 6).
[c]Relative merit across data types: scores from 1 to 3 have been applied to each data type. On the basis of the presented assignments, data from "Murine Models" has a greater relative merit (Score = 2) than "Osteosarcoma Target Biology/Expression" (Score = 1). It is understood that there may be novel drugs that do not have a dataset that includes all types of listed translational data.
[d]*Ex vivo* pulmonary metastases assay.
[e]Example, *in vitro* models including scratch assay, Boyden chamber, cell adhesion assays, etc.
[f]Using the PM Score (within a data type) and the relative merit across data types, a cumulative relative dataset merit can be determined and compared between distinct translational therapeutic opportunities.

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trials. The recent endorsement of the details outlined in this article by the National Cancer Institute Pediatric and Adolescent Solid Tumor Steering Committee (PASTSC) will serve as a starting point for future discussions, which will lead to the potential integration of the proposed scoring system for the prioritization of novel agents planned for clinical evaluation in pediatric patients with osteosarcoma. Accordingly, there will be an opportunity over time to test, validate, and modify the scoring system prospectively. As a means to demonstrate the feasibility and future use of the scoring system, Table 2 provides examples for how the scoring system can be applied, in this case by using therapeutic agents that have been recently evaluated in patients with osteosarcoma. These agents include liposomal muramyl-tripeptide phosphatidyl-ethanolamine (L-MTP-PE) and inhaled granulocyte-colony stimulating factor (GM-CSF; refs. 36–38). On the basis of supportive preclinical data and phase II trials in osteosarcoma, L-MTP-PE was advanced to a phase III trial in osteosarcoma. The study included a factorial design using event-free survival (EFS). No improvement in EFS was seen within this factorial design; however, a subsequent *post hoc* analysis revealed an 8% improvement in survival in patients (36). All results, including the *post hoc* analysis of survival, were interpreted to be supportive of substantial evidence of effectiveness by the European Medicine Agency and led to the recent approval of this agent in Europe for patients with osteosarcoma. With a focus on the primary study endpoint of EFS, the U.S. Food and Drug Administration did not interpret the data to be supportive of substantial evidence for effectiveness and the drug was not approved. The score for L-MTP-PE, using our described scoring system (cumulative relative dataset merit), was 60. In the case of the second example, inhaled GM-CSF was advanced into a trial of first lung relapse osteosarcoma patients based on evidence supportive of the feasibility of inhaled cytokine therapy. In the first lung relapse population and within the constraints of the executed trial, there was no evidence of immune modulation or antimetastatic activity demonstrated in patients (37). The cumulative relative dataset merit score for GM-CSF was 26. On the basis of the two examples presented above, it is clear that a broad range in scores will be derived from the proposed scoring method. Indeed, it is reasonable that these broad scoring possibilities will allow the prioritization of novel agents and allow the hypothesis suggested by the proposed scoring method to be testable over time.

A Proposed Mechanism to Value and Prioritize Preclinical and Translational Drug Development Data

Target biology and expression

The most valuable drug targets, as they relate to the problem of metastatic progression are those with functions that are fundamentally linked to the pathogenesis of micrometastatic progression. It is optimal for these targets to be expressed in micrometastatic cells. Although there are initial targets that have been identified with these credentials, additional studies are needed to expand the list of potential target candidates. Tissues from metastatic lesions and matched primary tumor tissues from the same patients are not widely available at this time and would provide a broader understanding of target expression profiles and their dynamics during metastatic progression. Expanding existing biospecimen efforts to collect clinically annotated tissues throughout the course of disease presentation and progression is required to better understand the development of metastases in osteosarcoma (Table 1).

Drug mechanism of action and pharmacodynamics

It is likely that a more detailed understanding of mechanism of action (MOA), and associated pharmacodynamic markers of effective therapeutic exposure and target modulation in tumor and surrogate tissues will be needed for agents that target metastasis and metastatic progression compared with agents that may act on measurable disease. Because it is not likely that toxicity will be a primary determinant of dose selection with biologically defined therapeutics, an understanding of MOA and pharmacodynamics may be critical in the definition of drug dose and schedule. Furthermore, it is widely recognized that the complexity of the metastatic cascade is difficult to model *in vitro*, as such the use of multiple (distinct) *in vitro* or preferably *ex vivo* assays (i.e., pulmonary metastasis assay; PuMA; ref. 39) of metastasis should be considered for defining early evidence of therapeutic activity and more importantly to elucidate mechanisms of action for a metastasis-targeting therapeutic.

Preclinical and murine models

Data demonstrating the activity of a novel therapeutic agent, at pharmacologically achievable exposures in several distinct murine cancer models are considered important for the development of all cancer drugs. The use of experimental metastasis models (tail vein injection) that result in the seeding of lung with cancer cells are valuable to "screen" potential therapeutics; however, the use of orthotopic models of osteosarcoma that include surgical management of the primary tumor and spontaneous pulmonary metastasis should be prioritized as a means to more fully demonstrate the value of a therapeutic approach. Genetically engineered models of osteosarcoma have now been described and may be used in drug evaluation (15, 40). Genetically engineered and other syngeneic models will be essential for therapeutics that modulate the immune response as part of their mechanisms of action. It is understood that the magnitude of a therapeutic response will be part of the basis to prioritize one therapeutic outcome against another. As such, it is essential that the variables that influence the behavior of a model and therefore the magnitude of potential responses are considered (i.e., delivered cell number, background of the mouse strain used, and time of treatment initiation) when comparisons between studies (and between therapeutic agents) are made.

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Table 2. Use examples for the cumulative relative dataset merit of agents recently evaluated or in study in patients with osteosarcoma

Determination of the cumulative relative dataset merit of MTP-PE in osteosarcoma

Dataset type	Description of data	Progressive merit within a data type	Relative merit across data types	Cumulative relative dataset merit	Supporting references
Target biology/expression	Target is abundantly present in metastatic osteosarcoma samples	5	1	5	49
Drug mechanism of action and pharmacodynamics	Clear biologic rationale for activity specific for osteosarcoma	5	1	5	50, 51
Target modulation/pharmacokinetics	Target modulation linked to mechanism of action	5	2	10	52–54
Murine models	Demonstration of significant activity against one orthotopic spontaneous metastasis model	3	2	6	55
Canine models	Demonstration >50% improvement in EFS in dogs with micrometastatic osteosarcoma in a randomized placebo-controlled study design	6	3	18	56, 57
Pharmacokinetics	Evaluation of optimal dose and schedule in relevant patient population	4	1	4	58–60
Human clinical data	Safety of new agent demonstrated in combination with MAP (or similar) chemotherapy	4	3	12	61–62
Total cumulative relative dataset merit				60	

Determination of the cumulative relative dataset merit of aerosol GM-CSF in osteosarcoma

Dataset type	Description of data	Progressive merit within a data type	Relative merit across data types	Cumulative relative dataset merit	Supporting references
Target biology/expression	Expression in micrometastasis	5	1	5	49
Drug mechanism of action and pharmacodynamics	Drug and target biology linked to metastatic phenotype - Demonstrated in multiple *in vitro* models	1	1	1	
Target modulation/pharmacokinetics		0	0	0	
Murine models		0	0	0	
Canine models		0	0	0	
Pharmacokinetics	Optimal dose and schedule in relevant patient population has demonstrated	2	1	2	63
Human clinical data	Evaluation of optimal dose and schedule in relevant patient population	6	3	18	48, 37
Total cumulative relative dataset merit				26	

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Example 1: Cumulative relative dataset merit

Example: Determination of the cumulative relative dataset merit of a novel therapeutic for osteosarcoma translation

Dataset type	Description of data	Progressive merit within a data type	Relative merit across data types	Cumulative relative dataset merit
Target biology/expression	Expression in micrometastasis	4	1	4
Murine models	Demonstration of significant activity against experimental (tail vein) metastasis	2	2	4
Canine Models	In dogs with micrometastatic disease, demonstration of single-agent activity >8 months, or >24 months in combination with cytotoxic chemotherapy	3	3	9
Human clinical data	Evaluation of optimal dose and schedule in relevant patient population	4	3	12
Total cumulative relative dataset merit				29

Canine osteosarcoma

Beyond the well-recognized difficulties with drug development in osteosarcoma, an important opportunity has been delivered by nature through the spontaneous development of osteosarcoma in pet dogs (41). The opportunities of this comparative approach to cancer drug development have been reviewed elsewhere (42). Biologic, histologic, and genomic features of osteosarcoma in dogs and humans are highly similar and have provided a basis to evaluate novel therapeutics in dogs with osteosarcoma (43, 44). As part of the broader field of comparative oncology, translational drug development studies in dogs with osteosarcoma have been used to define dose and schedule for therapeutic agents through rigorous pharmacokinetic–pharmacodynamic endpoints that can involve serial biopsies of tumor and collection of biologic materials (i.e., normal tissue surrogates) before and after exposure to a novel therapeutic (16, 45). Modeling of such dose-finding studies for agents that target metastasis may be an important use of the dog as a model. However, the greatest value of the dog with osteosarcoma as it relates to this "Perspective" is the opportunity to conduct studies in the setting of micrometastatic disease. In such studies, dogs will undergo management of the primary tumor and then in the adjuvant setting receive investigational agents alone or in combination with conventional chemotherapy backbones that are similar to those used in human patients. Through the integration of imaging endpoints, metastasis-free interval or survival may then be used to evaluate and compare different doses and schedules of investigational agents. Through the availability of a multicenter consortium of veterinary centers led by the National Cancer Institute (Comparative Oncology Trials Consortium; https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home) and the high prevalence of osteosarcoma in dogs, multiple studies (or study arms) may be successfully accrued in a time period that would allow comparison and prioritization of agents for evaluation in human patients. It is likely that observed activity in the adjuvant setting in the dog model would provide the most compelling data for the value of a novel therapeutic that may target metastatic progression, and Example 1 demonstrates how the inclusion of Canine Models would be valued in the Cumulative relative dataset merit assessment.

Pharmacokinetics

The nature and type of pharmacokinetic data needed to advance an agent that targets metastatic progression is not likely to be different from conventional cancer therapeutics. In the preclinical setting, studies should be conducted at exposures that are likely to be achieved in human patients. It is reasonable that studies of distinct treatment regimens (dose-schedule) in patients may be important to optimize therapeutic responses in the adjuvant settings. It is also important that these exposures are safely maintained during what may be extended treatment intervals (i.e., during the period of minimal residual disease).

Human clinical data

For agents that target micrometastatic progression, early human clinical trials will continue to focus on tolerability. As part of the safety assessment of these agents, their use in the setting of a conventional osteosarcoma backbone (i.e., methotrexate, doxorubicin, and cisplatin) will need to be established. Furthermore, as noted above, it is reasonable that the duration of assessment of tolerability will need to be extended, given the expectation that novel agents that target metastatic progression may require prolonged treatment exposures. As described under pharmacodynamics, given the likely absence of response in a measurable tumor, early-phase human trials should optimally include pharmacodynamic endpoints that will provide confidence on the adequacy of exposure and of the potential effectiveness

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of the exposure in accessible biospecimens. Unlike many other cancer histologies, clinical trials that assess the activity of therapeutic agents against metastatic progression have been successfully completed and are currently under way in patients with osteosarcoma. These trials including the evaluation of MTP-PE (46), GM-CSF (47), and a src tyrosine kinase (SARC012; http://sarctrials.org/Open-SARC-Trials) inhibitor were possible, given the unique pattern of metastatic progression in patients with osteosarcoma that includes the lung as a target organ and the fact that surgical resection of metastases is considered to be part of the standard of care. As novel trial designs are considered, there is a need to prioritize longitudinal endpoints of survival and metastasis-free interval and to ensure that accrual and completion of studies can occur in a reasonable time based on careful consideration of eligibility criteria and inclusion of multiple partners, including both pediatric and adult oncology (9).

Conclusion

Improvements in long-term outcomes for patients with osteosarcoma require a drug development path that prioritizes agents with activity against metastatic progression and not necessarily regression of measurable lesions alone. This approach may also improve outcome for patients with more common cancers too. The successful development of such agents demands a rigorous preclinical dataset, as we may not rely on early human clinical trials of tumor regression to support the development of these potentially valuable therapeutic agents. This "Perspective" provides reasonable guidance to consider and prioritize such preclinical data in osteosarcoma. The use of these guidelines will assist investigators in conducting studies that are believed to be most valuable in the assessment of agents that uniquely target metastatic progression. Similarly, the use of these guidelines will allow more consistent evaluation and comparison of potentially active agents as they are considered for clinical translation. It is reasonable that after sufficient experience is gained through the use of these guidelines that improvements and refinements can be made so as to optimize the preclinical and translational development of drugs in osteosarcoma.

Disclosure of Potential Conflicts of Interest

C. Khanna is an employee of Laboratory Link LLC. R. Gorlick is an employee of Oncolytics Inc. P.S. Steeg reports receiving commercial research grants from GlaxoSmithKline and Sanofi. S.R. Patel reports receiving other commercial research support from Astex, Eisai, Infinity, Johnson & Johnson, and Morphotek, and is a consultant/advisory board member for GlaxoSmithKline, Johnson & Johnson, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

This research was supported by the Intramural Research Program of the National Cancer Institute, NIH, Bethesda, Maryland. This research also was supported by the Chair's Grant U10 CA98543 and Human Specimen Banking Grant U24 CA114766 of the Children's Oncology Group from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Additional support for research was provided by a grant from the WWWW (QuadW) Foundation, Inc. (www.QuadW.org) to the Children's Oncology Group.

Received September 18, 2013; revised March 25, 2014; accepted April 13, 2014; published OnlineFirst May 6, 2014.

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Clin Cancer Res 2014;20:4200-4209. Published OnlineFirst May 6, 2014.

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