

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Measuring Drug Response in Sarcoma

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H&O How has response traditionally been measured in sarcoma and why does this need to change?

RB As with most solid tumors, sarcoma responses to therapy have traditionally been measured by the Response Evaluation Criteria in Solid Tumors (RECIST). These criteria require a 30% decrease in the maximum diameter of the tumor in order for the patient to be considered responding to chemotherapy. This 30% designation was arbitrary. The measurement is derived from the 50% shrinkage of perpendicular diameters of tumors noted in the World Health Organization response criteria, which in turn dates back to the original description of response by Dr. David Karnofsky in the early 1960s. In the early 1970s, Mortel and Hanley published their findings that considering a 25% decrease in tumor size to be a response to therapy resulted in error in 25% of cases, according to physical examination of spheres placed between foam rubber pads. However, a 50% shrinkage had only a 7% error rate. The criterion of a 50% decrease in size, which was translated into the unidimensional 30% decrease by RECIST, is based on the limitations of physical examination. Today, physical examination is almost never used to determine the size of tumors. The various imaging techniques that are now available are far more accurate, but the criteria have not been revised.

H&O Why does the size of the tumor not directly correlate to response?

RB One of the assumptions made in RECIST was that the size of a tumor is directly proportional to the number

of cancer cells present. In sarcomas, this correlation does not exist. In addition to cancer cells, tumors may contain certain stromal components that are not malignant and that may not disappear even when tumor cells are destroyed. Also, when sarcomas are destroyed by chemotherapy, there is often necrosis within the tumor resulting in a decreased number of cells, but not necessarily a major change in the size of the mass. Even when a tumor is composed entirely of cancer cells, the physical matter does not completely disappear when the cells are killed; myxoid degeneration can remain that is not necessarily immediately removed by the body. This result is similar to what occurs in nodular sclerosing Hodgkin disease, in which the tumor may be destroyed but scar tissue remains. In sarcomas, the tumor may be destroyed but scar tissue, bone, or necrotic material often remain. Occasionally, there may be no physical remnant of the tumor, in which case the traditional response criteria apply quite well.

H&O In what specific types of sarcoma has this issue been explored?

RB The majority of the data regarding measuring drug response in sarcoma pertains to gastrointestinal stromal tumors (GISTs). In this setting, the response rate by major improvement on positron emission tomography (PET) scan was found to be much higher than the response rate by the traditional response criteria. It is known that the vast majority of patients benefit substantially from treatment; the traditional criteria significantly underestimate the number of patients who respond to therapy. For example, findings published by Dr. Haesun Choi regarding changes following imatinib (Gleevec, Novartis) therapy for patients with GIST point to important discrepancies with the current response criteria.

H&O In what other types of sarcoma has this issue been explored?

RB There are few data published regarding the validity of response criteria in sarcomas. At the 2006 Annual Meeting of the American Society of Clinical Oncology, Grosso and colleagues presented a study of trabectedin (ET743, Johnson & Johnson) in the treatment of patients with myxoid liposarcoma. Changes very similar to those

that we initially described in GIST were seen in a high percentage of patients.

H&O Other than by RECIST, how is drug response measured in sarcoma?

RB There are two approaches to measuring drug response, depending on the specific type of sarcoma. For pulmonary metastases, the most common form of metastatic sarcoma, the standard response criteria are generally used. However, based on our experience with GIST, the need for a 50% decrease in the perpendicular diameter or a 30% decrease in any single diameter is questionable. The important criterion is any shrinkage at all. So that there is some guideline in measuring response, we generally consider a 10% shrinkage to be clear evidence that the treatment is having some effect. If a tumor that was previously growing has stabilized, this is also encouraging, although it is not considered a good response to therapy.

In the abdomen, where response is measured by computed tomography (CT), the same criteria as are used with GIST are applied: shrinkage of the tumor (with a 10% decrease in size considered to be a response) or decreasing tumor density. A decrease in density is generally seen when a tumor becomes necrotic or undergoes necrosis or myxoid degeneration. A decrease in tumor density by 15% is considered evidence of a response.

When evaluating primary soft tissue sarcomas, decreasing activity as shown by PET scans is a good measure of response, as is decreased contrast enhancement as shown by magnetic resonance imaging, in a manner similar to what is observed with CT scans of abdominal sarcomas. Quantitative measures have not been studied, and thus there is no fixed percentage of decrease in contrast enhancement that is considered to be definitive evidence of response. Rather, response is considered in a more qualitative fashion. However, as stated above, with regard to shrinkage, a decrease by as little as 10% is considered evidence of response; a 30% decrease is not necessary.

Osteosarcoma is a special case. A response to therapy may be new bone formation, and obviously, bone does not shrink. Here, an increase in smooth bone formation is considered to be evidence of response, and this formation may or may not be accompanied by tumor shrinkage. Ultimately, substantial tumor necrosis on pathology, at least 90–95%, is the ultimate standard in osteosarcoma, regardless of tumor size.

The individual types of sarcoma all vary in terms of what specific type of evidence is used for measuring response. However, what unifies all of these types is that the standard criteria most likely do not apply to any, although they are still sometimes used.

H&O Have these measures of response been found to correlate with prolonged survival?

RB There are as yet no cases of these response measures correlating with survival. Our group recently presented data showing a very good correlation, in patients with GIST who were treated with imatinib, between the new response criteria that we are proposing and time to progression or survival, but not with the more traditional criteria. In other sarcomas, the only definite correlations made thus far is that response by RECIST does miss patients with true response proven by pathology, and that anything less than progression according to RECIST may be an indicator of response.

H&O Are new criteria being developed?

RB Yes. There was a discussion last year during the Connective Tissue Oncology Society meeting, and continued efforts to develop response criteria for sarcomas are ongoing. The RECIST criteria will also be revised, or they may be eventually eliminated from clinical practice.

H&O Is the same discrepancy between RECIST-defined response and actual response seen in other cancer settings?

RB The same discrepancies most likely exist. Data were presented at the recent ASCO meeting in the setting of lung cancer, for example, showing that response was not important in terms of outcome, but absence of progression was key. In renal carcinoma, a study found that response was not a meaningful measurement even when there was a major difference in overall survival observed between two treatment arms. Using the criteria we are currently using for GIST, that study could have been predicted to be positive.

Suggested Reading

- Karnofsky DA. Meaningful clinical classification of therapeutic responses to anti-cancer drugs. *Clin Pharmacol Ther.* 1961;2:709-712.
- World Health Organization. *Handbook for Reporting Results of Cancer Treatment.* Geneva Switzerland: WHO Offset Publication;1979:48.
- Moertel CG, Hanley JA. The effect of measuring error on the results of therapeutic trials in advanced cancer. *Cancer.* 1976;38:388-394.
- Therasse P, Arbuck S, Eisenhauer E, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205-216.
- Choi H, Charnsangavej C, Faria SdC, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. *Am J Roentgenol.* 2004;183:1619-1628.
- Grosso F, Demetri GD, Blay JY. Patterns of tumor response to trabectedin (ET743) in myxoid liposarcomas. *J Clin Oncol.* 2006;24(18 pt 1):522s. Abstract 9511.