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EDITORIAL

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Clinical response versus clinical benefit in oncology: not necessarily equivalent terms

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One of the important distinguishing features of physicians who are considered to be *oncologists* is the requirement that they understand cancer management in terms of *overall goals* of treatment, as well as the risks and benefits of *all* reasonable therapies in a particular clinical setting. This focus is often far more complex than the rather simple question of whether a certain procedure (i.e., surgery) can be performed successfully.

For example, while it may be possible to remove a primary lung cancer in a patient with documented metastatic disease to the bone, the surgical oncologist will (or should) recognize the limited impact such a surgery will have on the individual's survival and quality of life. Similarly, while third-line chemotherapy can certainly be administered to a patient with refractory non-small cell lung cancer, the medical oncologist will (or should) understand the futility of such an approach.

In certain cancers the legitimate overall goal of therapy is cure. In such a setting, the oncologist recognizes it is reasonable to ask the patient to undergo considerable short-term toxicity (e.g., emesis, stomatitis), and even the potential for death (e.g., sepsis as a consequence of grade 4 neutropenia).

In this setting the oncologist does not necessarily need to be concerned with evidence of disease response. In the absence of documented progression, treatment is continued. For example, in a patient with breast cancer undergoing adjuvant chemotherapy, there will be no indication of clinical benefit, even if the individual is ultimately cured of the malignancy.

Conversely, when palliation is the goal of therapy, the aim of treatment should be to *minimize* the toxicity of treatment and *maximize* the quality of the patient's remaining life. In a patient receiving therapy will palliative intent, improvement in cancer-related symptoms felt to be secondary to the treatment program will be sufficient information to justify continuation of therapy (e.g., reduction in painful ascites in a women with ovarian cancer). However, evidence of excessive treatment-related symptoms in this clinical setting should be an indication to modify therapy, even if there is evidence of symptomatic benefit.

In making this determination of "successful therapy", it is important to distinguish symptomatic improvement due to antineoplastic therapy from that related to *direct* symptom management. For example, a decrease in right upper quadrant pain in a patient with metastatic cancer in the liver may be the result of a shrinkage of a tumor mass following the administration of cytotoxic chemotherapy, or may be related to the appropriate use of long-acting narcotic analgesia.

The oncologist is often required to employ a *surrogate marker* to evaluate the benefits of treatment in an individual patient. In the absence of specific symptoms, shrinkage of a tumor mass is frequently employed as a measure of "clinical benefit.

In fact, in the clinical trials arena, reduction in the size of a cancerous mass or nodule is often the only indication of clinical benefit. This is particularly the case with phase 2 clinical trials where the percentage of patients experiencing a complete (disappearance of all measurable disease) or a partial (50% reduction in the size of all measurable disease) response is considered the "gold standard" for evaluating the clinical utility of the drug(s).

Unfortunately, evaluation of symptomatic improvement in such studies is usually a secondary endpoint, if considered at all. It is well recognized that it is far easier to *quantify* a change in the size of a mass lesion, than it is to evaluate a reduction in pain, or improvement in fatigue or appetite. However, the question remains: Is it appropriate to equate *clinical response* to *clinical benefit*?

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Investigators who have examined quality of life in patients participating in cancer clinical trials have noted that there is often, at best, a poor correlation between the "objective response rate", as measured by a reduction in the size of tumor masses, and carefully designed patient questionnaires examining the patient's quality of life. Why should this be?

It is well recognized that quality of life is influenced by many factors, in addition to tumor-related symptoms. Toxicity of treatment, including fatigue and pain (e.g., chemotherapy-induced peripheral neuropathy) may mask a patient's perception of a decrease in cancer-related symptoms associated with a reduction in the volume of tumor.

However, it is also appropriate to consider the possibility that a reduction in tumor mass, particularly a partial reduction in areas where the tumor can be measured, may actually be associated with only a very small decrease in the total body burden of cancer. In addition, this "reduction" in volume may not occur in the regions of the body causing the most troublesome symptoms to the patient.

For example, a patient with gastric cancer with diffuse abdominal carcinomatosis may exhibit a 50% decrease in the size of a measurable metastatic lesion in the liver. However, if there has been no significant reduction in the volume of disease within the abdominal cavity (as is the most common outcome following the administration of chemotherapy in this setting), symptoms of early satiety, abdominal bloating and pain, will likely not improve.

Conversely, it is certainly possible that a patient can experience major symptomatic benefit from the administration of a chemotherapy program which fails to cause a "50% reduction" in the size of measurable tumor masses. Consider, for a moment, the same gastric cancer patient noted above. If this patient were entered onto a phase 2 clinical trial and experienced a major reduction in pain (not related to the administration of pain medications), an improvement in appetite, and weight gain, but failed to demonstrate at least a 50% reduction in the size of the hepatic lesion, the individual would be considered a "non-responder" (by standard criteria for measurable disease) to this treatment program. Is this a rational conclusion?

A significant reduction (e.g., 50% decrease) in the size of a tumor mass following the administration of a cytotoxic drug is clear evidence of a biological effect of the antineoplastic agent. This "clinical response" may be associated with an improvement in tumor-related symptoms, and ultimately result in a modest or major impact or survival. The "measurable response" will also likely have an important emotional effect on patients, their families and the physician.

However, it must be remembered it is inappropriate to simply assume that an observed clinical effect ("tumor shrinkage") is equivalent to clinical benefit. The questions must always be asked: "Has this biological effect of antineoplastic cancer therapy truly benefitted the patient?" Unfortunately, all too frequently, the answer to this question is that it has not.