The benefit of clinical benefit: A European perspective

Although the ultimate aim of treating the cancer patient is cure, in most metastatic solid tumors this, unfortunately, can only infrequently be achieved with chemotherapy. However, potential benefits such as palliation of symptoms or prolongation of survival, are other reasons for using chemotherapy for solid tumors. For the latter, assessment is relatively simple and hardly subject to discussion. However, how can we most appropriately evaluate other potential benefits?

Most medical oncologists will be familiar with the use of objective tumor regression to establish response. The measurement of response has clearly improved since the WHO in 1979 [1] issued its handbook for reporting results of cancer treatment. Even the quite straightforward tumor response criteria given in these guidelines have recently appeared limited. With the introduction of sophisticated techniques such as CT scan and MRI it has become possible to describe response in greater detail. This detailed information may well be the reason why over the years response to chemotherapy seemed to decrease while treatment remained unchanged [2]. Moreover, despite the amount of information presently available, determination of response suffers from interobserver variability. With the recent advent of reviewing the objective responses reported in clinical trials with new drugs it has become apparent, that in their enthusiasm about the activity of the new drugs, investigators overestimate the clinical response obtained. In other words, reports of even objective tumor regressions should be interpreted with caution. Another limitation to assessment of objective regression is that for many diseases even objective regression of disease is not appropriately reflected in a prolongation of survival. The justification for nevertheless applying chemotherapy in these cases is that most medical oncologists believe that objective tumor regression also results in a decrease of tumor-related symptoms. Therefore, additional tools for properly investigating the palliation of symptoms are of importance. For many years quality-of-life assessment with all of its limitations, has been used for this purpose.

In this issue of Annals of Oncology Rothenberg et al. [3] report on a phase II trial of gemcitabine in patients with refractory pancreatic cancer using the newly introduced 'clinical benefit response' that is presently under consideration by regulatory authorities for drug registration purposes. Despite the fact that objective tumor regression was scarcely mentioned, the authors report that a considerable number of patients benefited from treatment in other respects. The use of clinical benefit response as an endpoint of phase II studies is new and very interesting, but several considerations need to be taken into account when interpreting those data. Clinical benefit response was defined by the authors as $\geq 50\%$ reduction in pain intensity, and/or $\geq 50\%$ reduction in daily analgetic consumption, or $\geq 20\%$ improvement in the Karnofsky performance scale that was sustained for $\geq 4$ consecutive weeks, or a weight gain of $\geq 7\%$. The first 2 parameters were considered together and the other 2 as independent factors. If one of the factors was judged to be negative the patient was considered a non-responder, but if only one of the factors was positive and all of the others were stable the patient was classified as a responder. The use of reduction in pain intensity carries a subjective element, even though VAS scales were used. Moreover, the recording of daily analgetic consumption will depend on patient compliance. All medical oncologists are aware that there is a chance of their being misinformed because of the patients' desire to please the physician by giving answers they assume the physician wants to hear. Patients with malignant disease in the terminal phases of their lives are known to be especially prone to misleading the physician because of their hope for continued good treatment.

Even the Karnofsky performance score carries a subjective element. The score is partially dependent on the experience of the investigator and his or her attitude toward and belief in the treatment applied. Because of this, simplified performance scales have been introduced over recent decades. If we consider the other side of the coin, the potential clinical benefit should also be balanced against the potential negative effects of the chemotherapy, i.e., the side effects. Accurate reporting of side effects is another issue that was recently identified as difficult [4, 5]. It is known that physicians tend to exaggerate the severity of side effects when it is based on subjective measurements. In order to try to reduce this element the formerly used WHO criteria for toxicity were recently largely replaced by the much more detailed Common Toxicity Criteria issued by the U.S. NCI [6]. Still, even accuracy in reporting toxicities does not guarantee their being placed in proper perspective. The recent introduction, for instance, of 5-HT3 antagonists has created the impression among health care workers that nausea and vomiting have become less of a problem for cancer patients. It is worthwhile to note that patient perception appears to be the opposite of that of health care workers [7]. In other words, the latter study shows that while we believe that nausea and vomiting are less important, the patients still consider them to be the worst side effects.

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of chemotherapy. This demonstrates the difference in perception of symptoms between health care workers and patients and is another reason for caution in evaluating assessment tools that have a subjective element.

Even with these restrictions clinical benefit may well become a very important and relatively simple tool for measuring the effects of chemotherapy. To properly investigate this, randomized studies are required, as in fact the authors themselves indicated. Moreover, an appropriate comparison with existing tools such as quality-of-life measurements should be performed. Thirdly, a cost-effect analysis becomes important in an era when new chemotherapeutic agents are becoming increasingly expensive. An accurate balancing of the effects against the costs and comparison of the results with standard means of palliation appears to be warranted. Lastly, it may be difficult to project the results obtained in studies like these from one geographic region to another. Cultural differences in perception of the effect of treatment are a known entity. There is also an impression that there is a difference even between the two sides of the Atlantic in the tendency of patients to accept the inevitable evolution of their malignant disease. Patients who have difficulty in coping with the idea of dying will tend to ask for more (of dubious efficacy) treatment than those accepting of their ultimate faith.

Clinical benefit deserves to be investigated further in appropriately designed studies, also for validation of the tool itself. Until more data on these issues are available, the interesting results of studies such as the one presently reported by Rotherberg should be interpreted with caution. Just how beneficial 'clinical benefit' actually is has yet to be determined.

References