Gemcitabine for pancreatic cancer: How hard to look for clinical benefit? 
An American perspective

One of the objectives of clinical cancer research is to provide evidence of effectiveness of new anticancer agents for purposes of drug approval. In 1991, O'Shaughnessy et al. [1] published an important commentary illustrating a variety of endpoints that could be used by the United States Food and Drug Administration as the basis for approval of new anticancer agents for specific clinical situations. Although the ultimate objective would be to demonstrate a clinically significant survival advantage, other endpoints, including beneficial effects on disease-related symptoms and/or quality of life, could constitute clear clinical benefit and represent evidence of effectiveness. The guiding principle for drug approval is that the beneficial effects of an agent should sufficiently outweigh the adverse effects to achieve a favorable risk/benefit ratio for an individual patient; demonstrating net clinical benefit is sufficient for anticancer drug approval.

Responding to the opportunity to use disease-related symptom relief as an endpoint, Rothenberg et al. [2] report in this month's *Annals of Oncology* the outcome for 63 patients with pancreatic cancer who received gemcitabine after their disease had progressed despite prior treatment with 5-flourouracil. The study was sponsored by the drug's manufacturer (Eli Lilly and Company). A new endpoint, Clinical Benefit Response, was defined as a 50% or greater decrease in pain intensity (based on a patient self-assessment visual analogue scale), or a 50% or greater reduction in daily analgesic consumption, or a 20 point or greater improvement in Karnofsky performance status that was sustained for at least 4 consecutive weeks, and without worsening of any of these components. Weight gain of 7% or more was used to determine clinical benefit response if all of the other three elements were stable. Seventeen of the 63 patients (27.0%) achieved a Clinical Benefit Response to gemcitabine (95% CI, 16.0% to 38.0%).

Gemcitabine was reviewed by the FDA Oncologic Drugs Advisory Committee (ODAC) on July 24, 1995. I am an ODAC member who was widely quoted in the trade press and other publications that monitor the ODAC proceedings as making an enthusiastic comment: "I want to congratulate the company for putting in a lot of careful effort into a very difficult area of trying to define these kinds of endpoints in a rather conservative way" [3, 4]. It was not reported that I followed this compliment by raising several issues concerning the limitations of the Clinical Benefit Response endpoint: the subjective nature of patient self-reporting, the potential biases associated with early withdrawal from study, the lack of experience to interpret the true relevance of different Clinical Benefit Response rates and the need for double-blind randomized trials. Because the primary criteria for response is based on patient self-reports, some of the Clinical Benefit Response could reflect a 'placebo effect'. The endpoint requires follow-up to be long enough to allow a response to be observed. This was an issue for the randomized single-blind trial [5] of gemcitabine versus 5-FU which showed a 23.8% versus 4.8% difference in Clinical Benefit Response rates. The possibility that 5-FU recipients were removed from study more quickly by their physicians than gemcitabine recipients cannot be ruled out. Because Clinical Benefit Response is a new endpoint, it is impossible to interpret the relevance of a 27% Clinical Benefit Response rate. Although it appears to be a relatively high number given the disease setting, there are no data to calibrate this level of response rate with true net patient benefit for gemcitabine. Without a double-blind, randomized clinical trial it is not possible to evaluate the true effectiveness of the agent. The Clinical Benefit Response algorithm is a complicated, multi-component definition that requires serial assessment of pain intensity, analgesic usage, Karnofsky performance status and weight gain. For the assessment of the patients with pancreatic cancer, what was the basis for response for the seventeen patients who had a Clinical Benefit Response? Fourteen of the seventeen patients (82%) had a positive response based on pain category: 3 had improvement in pain intensity and improvement in analgesic consumption, 5 had improvement in pain intensity with stable analgesic consumption, and 6 had stable pain intensity but improvement in analgesic consumption. Three additional patients who were stable based on pain category were classified as clinical benefit responders based on improvement in Karnofsky performance status. Thus, in the case of gemcitabine for advanced pancreatic cancer, Clinical Benefit Response was essentially improvement in pain. A question concerning drug efficacy remains: Could such a response (primarily pain relief) have been achieved by means other than gemcitabine?

The median survival was only 3.85 months, and 85% had died within 7 months. Eight patients had extension to regional organs or lymph nodes without distant metastases. One patient had survived 4.4 years since the end of 5-FU and the start of gemcitabine.
There is no evidence from this study that gemcitabine extended the survival of these patients.

Perhaps the most difficult issue in defining net patient benefit is that the quality of life it seeks to evaluate is confounded with the duration of survival available to the patient. Performing treatment comparisons based on the amount of time the patients spend in clinical health states characterized by relatively good quality of life might be a better indicator of net patient benefit than defining a percentage of patients who achieve some criteria of response. Specifically, one might consider the amount of time patients are able to spend in a relatively good clinical status where pain intensity, analgesic consumption, Karnofsky performance status, and weight gain are used as the components to define the relatively good state. This approach is similar to that used for the Q-TWiST method [6, 7] (Quality-adjusted Time Without Symptoms of the disease or Toxicities of treatment) which compares treatments on the basis of quality-adjusted survival times; the preferred treatment is the one which provides more time with better health status (including considerations of both disease- and treatment-related events that reduce the quality of life).

Criteria for response to cancer therapies are subject to criticism, whether those criteria are subjective (even if systematically evaluated) or objective. We should recall that even our 'objective' criteria based on changes in tumor measurements are indeed subject to substantial measurement error [8]. The fact that treatments which produce higher response rates do not always yield better overall survival (in randomized comparisons) also argues against putting too much stock in estimating response rates as a guide to net benefit.

Seventeen patients had Clinical Benefit Response in this study. As is the case with most reports on anti-cancer drugs (especially those thought to provide some benefit), this study claims that the treatment was "generally well-tolerated with a low incidence of grade 3 and 4 toxicities". With respect to hematologic toxicity, 16 patients had grade 3-4 granulocytopenia, 7 patients developed grade 3-4 anemia, 11 patients received red blood cell transfusions. Clinical toxicities were also encountered: 18 patients had transient vomiting, while another 4 patients required antiemetic therapy and 1 patient had persistent vomiting despite antiemetics. Six patients had a grade 2 skin rash, 17 had fever in the absence of infection, and 10 had fever accompanied by headache, myalgia, chills, and asthenia. Nine patients experienced minimal alopecia and 1 developed patchy alopecia. Thus, although the toxicities were reported as moderate, more patients had some noticeable adverse experiences than achieved a clinical benefit response. A question left unresolved by the phase II study is whether many of these signs and symptoms were disease-dependent rather than treatment-induced.

It is not clear whether the current criteria for Clinical Benefit Response is indeed acceptable to the FDA. There is still much controversy concerning whether evaluations based on pain relief and performance status alone reflect a wide enough range of domains to adequately capture the patients' assessment of their quality of life. There has been much progress made to obtain validated quality-of-life assessment instruments for cancer patients. Such instruments should be used to assess the changes in quality-of-life dimensions other than just pain and performance status: physical well-being, emotional well-being and social functioning might also be assessed during the last months of life. Assessment of these other quality-of-life domains is required to indicate the extent to which Clinical Benefit Response is associated with improvements in global patient well-being.

The goal of palliative cancer therapy is to maintain the best possible quality of life for the patient for the longest possible time. Even in the palliative setting such as advanced pancreatic cancer, with 80% of the patients dying within six months, the availability of new treatment options can provide patients and their families with a spiritual uplifting based on renewed hope and a sense of control. In such dire situations it might even be more important than ever to balance the quality-of-life tradeoffs.

Is gemcitabine efficacious? Seventeen of 63 patients (27%) had improvement in pain status or performance status. About the same number suffered what are termed moderate subjective adverse experiences. The evidence of substantial benefit for gemcitabine is certainly not overwhelming.

Is there a way to answer some of these remaining questions concerning the usefulness of the Clinical Benefit Response and the efficacy of gemcitabine for patients with pancreatic cancer? Clinical investigators and pharmaceutical sponsors must be encouraged to build on this experience by using the important tool of randomization to define comparison groups. Some other types of innovative treatments should be considered for comparison with the 'novel' drug. Options for control arms in the randomized clinical trial could include 5-FU regimens which increase the availability of the drug in the neoplastic tissue, or other treatments with alternative mechanisms to control tumor growth such as the combination of low-dose octreotide and tamoxifen [9]. This would allow comparison of gemcitabine with treatments which cause few side effects. For desperate patients the evidence provided by the Clinical Benefit Response might be enough to justify the side effects and cost of gemcitabine for those patients in search of hope and relief of pain. Randomized clinical trials are needed, however, to better define the risk:benefit ratio of gemcitabine in this clinical setting.

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