

Does Palliative Chemotherapy Palliate?

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Does palliative chemotherapy palliate? This is a most provocative, complex, and highly clinically relevant question, with no simple answer. Before attempting to provide a meaningful response, it is important to understand what one means by the term “palliate.”

In the context of the current discussion, the Britannica World Language Dictionary defines the word “palliate” as “to relieve the symptoms or effects of without curing.” If this is an acceptable general interpretation of what is required to “successfully palliate” a patient with advanced cancer, it should not come as a surprise that it is rather easy for clinicians, and clinical investigators, to claim they have been “successful” in achieving this goal following the administration of cytotoxic chemotherapy.

Defining ‘Successful Palliation’

Given the “relieve the effects of” portion of this definition, *successful palliation* may be considered limited shrinkage of tumor documented by physical examination or radiographic evaluation, or even a decline in a serum tumor antigen level (eg, PSA, CA-125), which permits a patient to “feel the tumor is responding and the cancer is in retreat”. That this “success” may be achieved at the cost of substantial chemotherapy-associated emesis, fatigue, mouth sores, diarrhea, or infection may be considered irrelevant, or of limited importance *to the patient*, as long as the *biological effects* of the cytotoxic therapy against the cancer can be documented.

What if the disease in a patient with advanced cancer does not respond to chemotherapy, but remains “stable” for some period of time, and the level of toxicity is not “excessive.” Has this treatment produced a *palliative effect*?

Or consider the patient who has failed to respond to multiple chemotherapy regimens, and wishes to continue treatment, for not to do so would be “to give up and die.” If the administration of chemotherapy, or participation in a *clinical trial*, allows the patient to maintain *hope*, can this treatment be considered to have provided an element of palliation?

It is increasingly recognized that individual patient response to cancer, and its possible management, is remarkably variable [1, 2]. This tremendous heterogeneity is also evident in the philosophy of individual oncologists, who may approach therapy of patients with similar clinical characteristics in identical circumstances with vastly different expectations [3].

Patient Misunderstandings

In addition, studies have documented that despite extensive discussions, patients often fail or refuse to understand the fundamental goals of participation in highly experimental phase I clinical trials, or of the legitimate aims of palliative chemotherapy [4–8]. For example, in one survey, one third of 48 patients receiving *palliative treatment* “believed that the doctor’s aim was to cure them,” and over 80% of patients “significantly overestimated the probability that the treatment would prolong their lives” [7].

In another study, 42% of patients receiving palliative chemotherapy for ovarian cancer indicated treatment was designed to *cure their disease* [8]. This “optimistic bias” regarding personal risk appears to be a common human characteristic and is certainly not limited to how patients with cancer approach their illness [9].

Is it wrong for patients to elect to receive, and for oncologists to offer, chemotherapy that has an extremely small chance to achieve *objective* clinical benefit, if there is reason to believe such therapy may result in at least subjective improvement in the patient’s *sense of well-being* eg, “I am doing something about my disease, and not just waiting for it to kill me”?

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There are no easy answers to this question.

Perhaps a major reason for this dilemma is that it is simply not possible to provide a general answer to the issue of the palliative benefits of chemotherapy. Rather, to appropriately address this question one must inquire as to the potential palliative benefits of a *specific regimen*, for a *specific patient*, in a *very specific clinical setting*.

The disease, known activity and side-effect profile of available agents, unique clinical features (eg, preexisting heart or kidney disease), individual patient expectations (eg, “will do anything to live even a month longer”) and goals (eg, “wanting to live long enough to be able to attend a daughter’s wedding”), and the level and type of toxicity the patient will accept all play an important role in defining the potential for chemotherapy to produce *effective palliation*.

Each Situation Is Different

For example, studies have shown that patients will be willing to tolerate a high degree of certain kinds of toxicity (eg, pancytopenia, fatigue), while even mild or moderate levels of other side effects (eg, nausea and vomiting) are unacceptable [10]. However, the importance of each negative factor on the willingness of an individual patient to receive treatment is highly variable.

Thus, this argument leads to the conclusion that the potential palliative effects of cytotoxic chemotherapy simply cannot be defined adequately outside the context of an individual patient experience.

While one can certainly talk about the impact of chemotherapy on symptom-free and overall survival for a *population of patients*, based on the results of randomized phase III trials, and can even demonstrate that a chemotherapy strategy which produces limited shrinkage of tumor in only a minority of patients (eg, non–small-cell lung cancer) results in a superior survival outcome, compared to “best supportive care” (without the administration of chemotherapy) [11,12], this information does not necessarily provide information on the palliative benefits of chemotherapy in an individual patient.

The Difficulty of Applying General Findings to Specific Patients

To protect patient safety, and to establish a more homogeneous study population, the trials that ultimately define the “*standard of care*” for the treatment of advanced cancers will have required spe-

cific, mandated *exclusion criteria* for individuals with a marginal performance status, those who have significant comorbid medical conditions (eg, a history of severe chronic obstructive pulmonary disease), or patients who have received prior therapy (eg, adjuvant treatment for colon or breast cancer).

Thus, for a specific patient being considered for treatment with palliative chemotherapy, there is often the critically important question of how well do these published data apply to *this individual*? Will the potential survival benefits (in most metastatic solid tumors, the “advantage” being measured is a maximum of several months) justify the demonstrated toxicity?[13]

Further, it is only recently that the issue of the *quality of life* of patients participating in large phase III trials has even been addressed. Thus, there will be little information available in the oncology literature to answer the question of the relative benefits of treatment versus the negative impact of toxicity on the patient’s overall sense of well-being.

The point is that in the large majority of cancer chemotherapy trials (phase I–III), toxicity data have been, and continue to be, reported in almost complete isolation (eg, 15% incidence of grade 2 mucositis or diarrhea, 25% incidence of grade 3 thrombocytopenia), rather than *integrated* into an overriding evaluation of how any favorable impact of therapy on *cancer-related symptoms* might have been negated by the development of *treatment-related side effects*.

Balancing Symptom Relief Against Treatment Toxicity

For example, if the pelvic pain caused by the presence of a 6 cm pelvis mass is substantially reduced following chemotherapy, which results in a 50% reduction in the size of the lesion, are the palliative benefits of therapy nullified by the development of debilitating treatment-related mucositis or diarrhea? As an extension of this question, it should be asked if a similar degree of symptom relief could have been achieved with the appropriate use of narcotic analgesia without the production of these chemotherapy-associated side effects?

Finally, it is important to note, that issues of cost may be relevant for individual patients (eg, personal resources, insurance coverage) and for particular societies, where a universal coverage

system will be responsible for payment for the proposed palliative chemotherapy [14–16]. Both patients and societies may appropriately inquire if there are less costly, but perhaps equally effective, measures available to control symptoms of the malignancy.

In some clinical settings it is rather easy to argue for the *palliative benefits* of palliative chemotherapy, even without studies that have formally documented the favorable impact of such treatment on *quality of life*. For example, currently available data would support the statement that 60%–80% of individuals with previously untreated ovarian cancer or primary carcinoma of the peritoneum will achieve both *objective* (eg, decrease in ascites, pelvic masses, CA-125 antigen levels) and *subjective* (eg, decrease in pain, increase in appetite) evidence of improvement in the disease process following treatment with either single-agent carboplatin or the combination of carboplatin plus a taxane [17]. With this level of biological and clinical activity documented in large patient populations, and the generally acceptable toxicity profile for such therapy, particularly single-agent carboplatin, it is reasonable to argue that “palliative treatment” in such patients clearly *does provide palliation*.

Conversely, for the patient with metastatic pan-

creatic cancer, and many other advanced malignancies, who have already failed two, three, or four prior chemotherapy regimens, it is very difficult to argue for the demonstrated merits of continuing antineoplastic drug therapy.

But what if the patient *wants* more treatment?

Back to the Art of Medicine

In summary, this commentator would conclude that the ultimate answer to the question of the palliative benefits of palliative chemotherapy will not be found in an oncology textbook, the latest issue of a leading clinical or basic science journal, or the advertisements or pronouncements of a biotech or pharmaceutical company.

Rather, the answer will be determined only through *careful consideration* of relevant existing data from previously reported high-quality trials (eg, randomized phase III and selected phase II studies), *evaluation of individual objective clinical features* (eg, performance status, comorbid conditions, prior toxicity experienced by the patient), and the more *subjective parameters of patient expectations, anxieties, and goals*, and, finally, through *thoughtful discussion* between the physician and patient (often with other family members) regarding both the *potential palliative benefits* and *realistic harm* that chemotherapy may produce.

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