**Palliative Chemotherapy: No Longer a Contradiction in Terms**

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**Key Words.** Antineoplastic agents combined · Antiemetics · Cisplatin · Antimetabolites · Antineoplastic · Quality of life · Bronchial neoplasms

**ABSTRACT**

Palliative chemotherapy is defined as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage, but does affect improvement in terms of tumor-related symptoms, and where the palliation/toxicity trade-off from treatment clearly favors symptom relief.

The role of chemotherapy in circumstances where little or no survival benefit is anticipated remains controversial. This is despite the mounting body of evidence in favor of its use for symptom palliation. The notion persists that outcomes other than significant survival benefit are not valid, because of firmly held perceptions of toxicity.

Studies of chemotherapeutic palliation using valid measures of quality of life, show that patients may be willing to accept some side effects of treatment, as long as they gain relief from tumor-related symptoms.

The aims of this review are to present the case for palliative chemotherapy, to highlight the areas of progress which have made this feasible, and to provide guidance with regard to its appropriate use. *The Oncologist* 1999; 4:470-477

**INTRODUCTION**

The last 10-15 years have seen a gradual but important change in the perceived role of chemotherapy in the treatment of advanced cancers. During the 1970s and much of the 1980s, the majority of oncological trial protocols concentrated on evaluating response rates, disease-free intervals, and overall survival as endpoints. Although those involved in the treatment of advanced malignancy with intravenous chemotherapy frequently observed symptom improvement in their patients, the concept of “palliative chemotherapy” was almost a contradiction in terms. Even in advanced breast cancer (where effective palliation with chemotherapy has been possible for decades), this aspect of care is still frequently undervalued in papers which concentrate on highlighting modest effects on survival.

Our purpose here is to summarize the evidence supporting the notion of palliative chemotherapy, highlight the key developments that have contributed to its increasing importance and give some guidance on its clinical implications.

Palliative chemotherapy is defined as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage, but does affect improvement in terms of tumor-related symptoms, and where the palliation/toxicity trade-off from treatment clearly favors symptom relief. The balance between disease- and treatment-related symptoms forms the physical dimension of quality of life (QOL). Improvement in this parameter is likely to be followed by improvement in other areas leading to global improvement.

**STUDIES OF CHEMOTHERAPEUTIC PALLIATION**

**Colorectal Cancer**

The effect on QOL and palliation has been examined in two chemotherapy trials in colorectal cancer. Scheithauer et al. [1] conducted a small study in 36 patients with advanced colorectal carcinoma. They were randomized to receive either folinic acid modulated 5-fluorouracil (5-FU) with cisplatin or best supportive care only. The treatment group had a longer median survival and time to progression. Furthermore, those receiving chemotherapy had QOL scores which were either equal or better than those randomized to best supportive care alone, suggesting that receiving chemotherapy did not adversely affect patient’s QOL per se.
The Nordic Group conducted a controlled trial in asymptomatic patients with advanced colorectal carcinoma. They compared immediate 5-FU and methotrexate therapy with the same treatment delayed until symptoms occurred. Survival was better in those patients assigned to immediate treatment (median survival 14 versus 9 months), and symptom-free survival showed a similar trend (10 versus 2 months).

Performance status was maintained in both arms unless disease progressed. Clinical and radiological responses to treatment correlated with patients’ subjective assessment of symptom response. All patients with either a complete response or partial response gained a subjective response, and none of the patients with stable disease deteriorated symptomatically. Another disadvantage of treatment deferral in this group was the general decline in patient fitness associated with disease progression, rendering them unfit for potentially worthwhile treatment [2].

Breast Cancer

It is now widely accepted that the treatment of women with advanced breast cancer is palliative in its intent. Unfortunately, no randomized, controlled trials of chemotherapy versus best supportive care were conducted before chemotherapy for metastatic breast cancer was introduced. Such trials would now be considered unethical, as the response rate to first-line chemotherapy is so high (approximately 40%). The issue of QOL as an endpoint in chemotherapy trials in metastatic breast cancer is now being addressed by increasing numbers of workers [3]. No single regimen has emerged as being the “gold standard.” Anthracycline-containing regimens have a slightly higher response rate, but this may not correlate with better survival and QOL [4]. We do know, however, from published studies that cytotoxic-induced tumor shrinkage is associated in some women with symptom benefit and may prolong life [5]. It also appears that if the decision is made to start cytotoxic therapy, adequate doses should be employed. Two separate randomized studies have used standard dose CMF as their control arm against low-dose CMF and low-dose epirubicin, respectively [6, 7]. In both studies, despite higher levels of nausea, vomiting and myelosuppression, QOL was better in the standard CMF arm. In both cases the response rate was higher for the more intensive regimen.

Small-Cell Lung Cancer (SCLC)

The increasing recognition of the balance between desired and unwanted effects of chemotherapy has led some investigators to reduce treatment intensity in patients with incurable cancer in the hope of preserving the benefits while minimizing the side effects of treatment. Earl et al. [8] however, illustrate the importance of not staying too far in this direction by giving too little treatment. They randomized 300 patients with untreated, limited and extensive stage SCLC to receive regular chemotherapy three times per week or, “as required” chemotherapy for tumor-related symptoms, or if there was radiological evidence of progression after one cycle. Diary cards were kept by each patient in the trial: the ability to carry out activities of daily living and surrogates of general well-being such as mood and sleep patterns were recorded. The “as required” group reported more disturbance in the activities of daily living, and their overall feeling of well-being was less than in the regular chemotherapy group. This was despite the fact that the group which received regular chemotherapy experienced more treatment-related toxicity. It appeared that chemotherapy was more effective at palliating the tumor-associated symptoms when given regularly.

Oral treatment is often perceived as a less intense, less toxic option, but formal comparisons have generally failed to support this view. Etoposide, for instance, is one of the most active single agents for the treatment of SCLC, producing objective responses in at least 65% of patients with extensive disease when given orally. It is most often prescribed at a three weekly dose of 50 mg twice daily for 10 days. The UK MRC Lung Cancer Working Party prematurely closed a randomized trial comparing oral etoposide and standard dose VAC in SCLC, in 1995, after a total of 339 patients were randomized. The hematological toxicity was greater, and survival was significantly worse in the oral etoposide arm [9].

Pancreatic Cancer

Pancreatic carcinoma is a notoriously chemo-insensitive tumor [10, 11]. Early studies with gemcitabine in this disease noted stabilization and relief of tumor-related symptoms in about 25% of patients, despite only a modest impact on measurable response and survival [12]. This led to the concept of Clinical Benefit Response, devised by Rothenberg et al. [13] as a way of assessing palliative efficacy of chemotherapeutic agents, based on reduced pain intensity, lower analgesic consumption, and better performance status sustained over a four-week period. The toxicities of gemcitabine are generally mild and of short duration, ideal for a drug used for palliation.

The Balance of Risks and Benefits in Advanced Cancers: Limiting Toxicity

The use of palliative chemotherapy in patients with relatively chemo-insensitive tumors (eg., non-small cell lung cancer [NSCLC]) remains controversial, despite the accumulating body of evidence that its use is associated with symptom relief and a small survival advantage [14]. Historically, intravenous chemotherapy has been labeled as so toxic that effects other than substantial prolongation of life were regarded as not worth the potential risk. Progress in a number of areas is resulting in a gradual but definite re-evaluation of entrenched scepticism [15].
Advances in Antiemetic Therapy

Nausea and vomiting are among the most feared side effects of chemotherapy and weaken the resolve even of those undergoing curative treatment [16]. In the past this has been an obstacle to the selection of highly emetogenic drugs in palliative chemotherapy. The arrival of the 5-HT3 antagonists has transformed the emetic profiles of agents such as cisplatin, which may now be given to patients with palliative intent [17]. Ondansetron and granisetron, for instance, are well tolerated and their antiemetic efficacy is enhanced by the addition of dexamethasone at least in the acute phase. Individual patient characteristics coupled with the proposed drug regimen can allow the physician to assess the risk of vomiting (Table 1). In the case of multiple adverse risk factors, maximal antiemetic prophylaxis should be considered, even if moderately emetogenic regimens are being used.

Altered Mode of Administration of Cytotoxic Drug: Altered Toxicity Profile

The incidence of drug-related side effects may be further reduced by altering the mode of administration of the cytotoxic drug, or by selecting drugs with less toxicity. In colorectal cancer, for instance, 5-FU and leucovorin (5-FU/FA) remain the first-line treatment for metastatic disease. The toxicities associated with this combination are mucositis, diarrhea, nausea and vomiting, myelosuppression, rash and alopecia. De Gramont et al. [18] have demonstrated that the response rate and incidence of grade 3-4 toxicity are schedule-dependent. Four hundred and thirty-seven patients were randomized to receive either bolus 5-FU/FA days 1-5 every four weeks, or a 2-h infusion of FA, followed by a bolus of 5-FU, and a 22-h infusion of 5-FU on days 1 and 2, repeated every two weeks. There was less neutropenia and mucositis with infusional 5-FU (Table 2).

Selection of Drugs with Favorable Toxicity Profiles: Platinum Agents

In the UK carboplatin is routinely used as the platinum agent of choice in the treatment of advanced ovarian carcinoma, as it is less nephrotoxic, neurotoxic and emetogenic than cisplatin, and routine parenteral hydration is not required. Consequently it may be given in an outpatient setting. Response rates to cisplatin and carboplatin in ovarian cancer are similar [19].

It is, however, important not to assume that these agents are equivalent for all tumor sites. The UK MRC Testicular Working Party randomly allocated patients with metastatic testicular teratoma to receive standard cisplatin, etoposide and bleomycin, or carboplatin, etoposide and bleomycin as first-line treatment. The three-year survival rates were 97% and 90%, respectively. This statistically significant difference led the working party to conclude that at the given doses and schedules, combination chemotherapy based on carboplatin was inferior to that based on cisplatin [20]. This also appears to be the case in bladder cancer and head and neck tumors [21].

Treating the Elderly

The incidence of cancer in the general population rises steeply with increasing age. Three in every 100 men over the age of 60 develop the disease each year [22]. Older patients are more likely to have coexisting chronic disease and tolerate chemotherapy less well than younger ones. However, with careful attention to drug and dose selection, effective palliation is routinely possible in selected patients with chemotherapy-sensitive malignancies [23]. Those with ovarian and SCLC for instance, whose performance status is limited by tumor-related symptoms, may experience prompt improvement with judicious use of palliative chemotherapy (Fig. 1). Data are also emerging which demonstrate improved QOL with chemotherapy in elderly patients with NSCLC (see below), and that performance status gives a better indication of the potential for developing treatment-related complications than does patient age [24-26].

### Table 1. Risk factors for cytotoxic-induced emesis

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Drug-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe anxiety</td>
<td>Platinum agents</td>
</tr>
<tr>
<td>Female sex</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Age &lt;45 years</td>
<td>Nitrogen mustards</td>
</tr>
<tr>
<td>Prone to motion sickness</td>
<td>High-dose cyclophosphamide</td>
</tr>
<tr>
<td>Low alcohol intake</td>
<td></td>
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<tr>
<td>Taste disturbance during treatment</td>
<td></td>
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<tr>
<td>Emesis with prior cycles</td>
<td></td>
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</tbody>
</table>

### Table 2. Toxocities associated with two 5-FU-based regimens

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Bolus 5-FU</th>
<th>Infusional 5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>7.9</td>
<td>2</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Mucositis</td>
<td>9.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Table 2. Toxicities associated with two 5-FU-based regimens

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Percentage of patients experiencing grade 3 or 4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>7.9</td>
</tr>
<tr>
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<td>Rash</td>
<td>0.5</td>
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</table>
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burgeoning interest in chemotherapy for NSCLC, despite having no single drug capable of inducing a significant observable response in more than 20%-25% of cases [11, 27], and beneficial effects on survival even from the best combinations seem to be barely as long as the duration of treatment itself.

Ironically, the very first report of chemotherapy in lung cancer (in 1948) was titled: “The use of nitrogen mustards in the palliative treatment of carcinoma, with particular reference to bronchogenic carcinoma” [28]. The author was Karnofsky and it was in this paper that he first described his performance status scale which is still in use today. Interest in this area has probably been restimulated by the fact that, like Karnofsky, many investigators have witnessed worthwhile symptom improvement in their patients having chemotherapy for advanced lung cancer (Fig. 2). At the same time perhaps the best drug, cisplatin, has become much more acceptable with the arrival of effective antiemetics.

In 1986 we began work in Birmingham with mitomycin, ifosfamide and cisplatin (MIC). Our commitment to the project—which has culminated in two randomized trials including a total of over 800 patients—was fueled by the experience of many patients who said that they felt better since chemotherapy started. We also investigated QOL in a subgroup of these patients. Symptom change and side effects were compared in over 100 cases randomized to either chemotherapy or an alternative palliative treatment. Using a variety of analytical approaches, chemotherapy was superior [29].

Figure 1. A and B illustrate the clinical and thoracic CT appearances of an elderly man who presented with a chest wall mass and pain. Histology of the mass showed SCLC. C) The same patient after a course of palliative chemotherapy: his pain resolved promptly.
Others have reported symptomatic benefit in patients receiving moderate-dose cisplatin-based chemotherapy in studies of NSCLC [31], and conventionally defined complete or partial remissions are not essential for symptomatic response. Table 3 also shows data for symptom improvement with palliative radiotherapy, and single-agent gemcitabine [30-33, 41].

The latter is clearly active in NSCLC, and has a relatively favorable side-effect profile. Its arrival has contributed to the palpable momentum of palliative chemotherapy, and investigators have begun to evaluate its role in symptom relief. Furthermore, authorities considered QOL data in their licensing evaluation of gemcitabine. The new vinca alkaloid vinorelbine is also showing promise in the palliative treatment of advanced NSCLC. In a recent study, 350 elderly patients with advanced NSCLC were randomized to receive either single-agent vinorelbine, or best supportive care. Vinorelbine was better at relieving lung cancer symptoms, and its use resulted in a small, but statistically significant survival advantage [34].

Silvestri et al. [35] showed how highly patients value palliation when choosing between best supportive care and chemotherapy for NSCLC. They interviewed 81 patients previously treated with chemotherapy and showed that although only 22% of patients choose chemotherapy for a three-month improvement in survival, 68% would choose chemotherapy if it substantially reduced symptoms without prolonging life.

Table 3. Percentage of symptomatic patients reporting improvement following treatment for advanced NSCLC (adapted from Thatcher et al. [33]).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>XRT Reference</th>
<th>MVP Reference</th>
<th>PV + M or I Reference</th>
<th>MIC Reference</th>
<th>Gemcitabine Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>60%</td>
<td>71%</td>
<td>45%</td>
<td>70%</td>
<td>44%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>84%</td>
<td>–</td>
<td>91%</td>
<td>92%</td>
<td>63%</td>
</tr>
<tr>
<td>Pain</td>
<td>78%</td>
<td>63%</td>
<td>47%</td>
<td>77%</td>
<td>32%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>61%</td>
<td>65%</td>
<td>78%</td>
<td>46%</td>
<td>26%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>67%</td>
<td>–</td>
<td>50%</td>
<td>58%</td>
<td>29%</td>
</tr>
<tr>
<td>Response</td>
<td>30%</td>
<td>21%</td>
<td>42%</td>
<td>56%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Figure 2. A) Chest x-ray of a patient with NSCLC, showing a massive right hilar mass. She was profoundly short of breath at presentation. B) Chest x-ray of the same patient after four cycles of MIC chemotherapy shows a partial response to treatment. Her symptoms resolved with treatment.
EVALUATING PALLIATIVE CHEMOTHERAPY

Clinical Research

Evidence to support the use of chemotherapy for palliation must be assessed scientifically, ideally within randomized trials, using appropriate endpoints. QOL has become an important secondary endpoint in many clinical trials, but increasingly it will become a key primary endpoint. Symptom improvement in conjunction with treatment toxicity form the physical dimension of QOL. Other dimensions such as psychological, social, and sexual functioning will clearly be influenced by the effectiveness of the treatment in physical terms.

Unlike survival, measuring QOL is subjective, and there are a plethora of instruments available for the purpose [35]. Choosing an appropriate, valid and reliable instrument that will assess symptom improvement, and also evaluate the separate issue of treatment toxicity for the given disease site is essential. Some instruments focus on the physical aspects of QOL, but are not disease specific (Rotterdam symptom checklist [36]), while others have been written specifically for certain disease sites (disease-specific modules of the European Organization for Research and Treatment of Cancer questionnaire [37]). Although questionnaires are generally completed by the patients, they do not enable the individual to specify the factors that are important to their QOL. An alternative approach, the Schedule for the Evaluation of Individual Quality of Life [38] has been devised that allows the patient to nominate five facets of life on which to be assessed.

The analysis of QOL data can be problematic, especially in a palliative care setting. QOL studies are usually longitudinal in that patients are required to complete a series of questionnaires over a period of time. The completeness of data can be maximized by recruiting a dedicated research nurse to supervise and assist patients, but the problem of patient dropout through illness or death will remain, especially in the palliative setting. This results in non-random loss of QOL data. All standard, statistical methods for analyzing longitudinal data will be invalid in these circumstances, since they assume the missing data mechanism is random. Methods of analysis that simultaneously assess QOL and survival may provide a means for overcoming this problem [39].

Clinical Practice

Monitoring palliative chemotherapy in the clinic involves an assessment of the palliation/side effect balance prior to each cycle of chemotherapy using objective means such as symptom/toxicity flow charts. Patients should continue beyond one or at most two cycles only if there is clear palliation, and the associated toxicity is deemed acceptable by the patient. Conventionally defined complete or partial remissions are not essential for worthwhile palliation, but objective evidence of disease progression should always trigger discontinuation of chemotherapy.

Conclusion

The evidence in favor of palliative chemotherapy is steadily accumulating from well-designed randomized trials, and “best supportive care” may now be second-best. We are gaining deeper insights into the comparative associated morbidities of commonly used regimens, and the management of these side effects is improving with time. Palliative chemotherapy should be given as a therapeutic trial, and discontinued if there is no sign of symptom relief, or if there is unacceptable toxicity or evidence of disease progression. This prevents the accumulation of toxicity in patients who are not responding to treatment and allows the direction of resources towards those who are deriving real benefit. The cost effectiveness of this approach has been shown to be better than supportive care in one study in NSCLC [40].

Perhaps one of the most important advances in this field has been the trend towards asking the opinions of patients receiving treatment. It is now known that chemotherapy in the palliative setting need not be free of side effects: these side effects need only be tolerable and outweighed by symptom relief [6, 42]. QOL scores are now perceived as an integral part of clinical studies, and there is an urgent need for clarification and development of statistical methods aimed at making sense of and simplifying the numerical harvest of QOL data.

Far from regarding palliation as the last resort of the desperate oncologist, we should design trials specifically to test for symptom relief. Palliative chemotherapy is a reality in a number of advanced cancers; our challenge is now to affect a widespread change in attitude and practice.

References


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