

## Clinical Topics

# Cytotoxic chemotherapy for common adult malignancies: "the emperor's new clothes" revisited?

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Look Mummy, our Emperor has no clothes on!  
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A bewildering number of clinical studies on the efficacy of cytotoxic chemotherapy for various adult solid tumours has been reported. Enthusiasm among medical oncologists has been generated largely by the dramatic successes achieved by chemotherapy over the past 10 years in fairly uncommon malignancies, such as Hodgkin's disease, histiocytic lymphoma, germ cell tumours, choriocarcinoma, and various solid tumours of childhood. In addition, high rates of partial response are often achieved nowadays with combinations of cytotoxic drugs in several hitherto untreatable adult malignancies. The race to conquer cancer with drugs has been further intensified by the non-medical press and by energetic advertising programmes of pharmaceutical companies.

Despite the current wave of enthusiasm the vast majority of chemotherapy is given with palliative intent.<sup>1</sup> Thus a rational decision to use cytotoxic drugs must inevitably entail the often complex trade off between likely benefits and expected side effects (both physical and non-physical). The use of toxic, and therefore potentially fatal, cytotoxic drugs should be seriously questioned unless they are likely either to yield a high incidence of durable complete remissions (some leading to ultimate cure) or to cause such regression of advanced cancer that symptomatic relief affords a prolonged period of improved quality of life. Lamentably, however, not only is our ability to assess palliation and quality of life rather rudimentary but the current proliferation of trial results that cannot be properly evaluated (see below) may lead both oncologists and non-oncologists to overestimate the role of chemotherapy and, at the same time, to undervalue the impact of toxicity related to treatment. The problem is compounded by recent technological innovations and a current vogue for intensive investigations to characterise the malignancy accurately in terms of its biological behaviour and extent of spread. Such intensive investigation is often inappropriate to the patient's needs and makes it extremely difficult for the clinician not to "do something," even though he may know enough to appreciate that active treatment might well do more harm than good.

Lack of space precludes a discussion of all adult solid tumours, but I have examined here the current impact that cytotoxic chemotherapy is having in the treatment of the most common adult malignancies. To suggest reasonable recommendations on the role

of cytotoxic drugs and to define subsets of patients most likely to derive benefit from such treatment I have emphasised those studies from which meaningful conclusions can be drawn.

### Problems of partial response

Antitumour efficacy has been defined primarily in terms of some measurable reduction in the patient's total tumour burden. Many methods have been used to assess regression of tumour, which has been defined in several different ways. Indeed, subtle differences in the criteria for response cause large changes in apparent response rates. Tonkin *et al* expressed their concern about the wide disparity in reported rates of tumour response when patients with the same type of tumour are treated with similar cytotoxic regimens.<sup>2</sup> Indeed, serious methodological inaccuracies (including use of uncontrolled studies, small numbers of patients, varying cytotoxic doses and schedules, and inconsistent criteria for response) often make conclusions about the merits of a particular regimen impossible, ambiguous, or even erroneous.<sup>3</sup>

Except in the case of a few rare tumours in which specific biological markers accurately reflect tumour burden, clinicians must rely on the criteria of the International Union Against Cancer as an objective assessment of tumour regression.<sup>4</sup> Complete response is defined as "the disappearance of all known disease." Though a complete response is generally considered to be a prerequisite for ultimate cure, obtaining a complete response by no means guarantees cure. Partial response is defined as a response "greater than or equal to a 50% decrease in measurable lesions and objective improvement in evaluable but non-measurable lesions. No new lesions. It is not necessary for every lesion to have regressed to qualify for partial response, but no lesion should have progressed." Although not specifically recommended by the International Union Against Cancer, the minimum duration for both complete and partial responses is now generally accepted as four weeks.

Although few clinicians would doubt the therapeutic efficacy of cytotoxic regimens that produce a high incidence of durable complete remissions, much scepticism exists about partial responses. As Watson emphasised, a partial response is considered by many clinicians to be "far too crude an indicator on which to base the management of patients."<sup>4</sup> There is an increasing risk that falsely inflated rates of partial response, especially responses of short duration, are likely to misrepresent the impact of cytotoxic drugs and to lure medical practitioners into recommending (and using) toxic regimens that have little chance of providing a clinically useful remission for the patient. Although many clinicians refer to current rates of partial response achieved with cytotoxic drugs as being "exciting" for the future, even high partial response rates—for example, seen in head and neck cancer—are not generally being translated into improved patient survival.<sup>5</sup> The most important criticisms of the criterion for partial response are fourfold.

Firstly, from a cell kinetic standpoint, volumetric changes in a given target lesion may be influenced by many factors and can therefore yield only a crude indication of the cytotoxic efficacy of treatment. The size of any lesion reflects the variable cellular dynamics of residual dead cells, differentiating or end cells, and regenerating viable tumour cells (clonogenic cells) as well as stromal elements. In addition, it will be subject to both systemic factors—for example, hormones, general patient nutrition—and local factors—for example, surface exfoliation, physical constraints on



growth and vascular supply, immune and inflammatory cell responses. As the extent of the reduction in volume may equally be a function of the rate of removal of dead cells or of production of new cells, or both, changes in the size of a lesion are an unreliable index of killing of clonogenic cells. Because of the wide variation in tumour doubling times changes in the size of a lesion over such a short period of four weeks must be considered to be of dubious importance. Furthermore, neither complete nor partial response categories yield any useful information about the chemosensitivity of the all important clonogenic cellular compartment. The difference between a complete and a partial response after cytotoxic therapy is not necessarily related to greater killing of clonogenic cells in lesions exhibiting a complete response. In fact, there may be appreciable regeneration of clonogenic cells during regression of a target lesion.<sup>6</sup>

Secondly, the measurement of a particular lesion, say on a plain radiograph, may be altered by many factors, including magnification, orientation, penetration of the beam, configuration of the lesion, and the presence of coexisting disease. These same types of inaccuracies apply to measurements made from clinical examination, scintiscans, and lymphangiograms, or when bidimensional measurements are not possible. The importance of errors of measurement on reported response rates in clinical oncology was reviewed by Warr *et al.*<sup>7</sup>

Thirdly, in the presence of multiorgan disease, with some lesions responding and others not, the term partial response may be difficult to define.

Finally, attainment of a partial response, even if a limited reduction in the clonogenic tumour cell compartment actually occurs, does not necessarily correlate with relief of symptoms, improved quality of life, or useful extension of life. Although it may sometimes be of no benefit to the patient, a partial response may occasionally produce striking and very helpful relief of symptoms. This is especially so when tumour masses compress nerves or hollow structures—for example, the bronchus, oesophagus, or vena cava—and when a slight reduction in tumour size may considerably improve a patient's quality of life. Conversely, however, a patient may also gain appreciable symptom relief without a demonstrable reduction in the size of a target lesion.

Unfortunately, the term partial response has become entrenched in oncology, and alternative methods of expressing the same concept more meaningfully, yet simply, are urgently needed. Thus in this review I have emphasised rates of complete response for individual malignancies and discuss partial responses only when they seem to yield clinical benefit.

### Overall incidence of cancer and value of cytotoxic chemotherapy

The most recent statistics published by the National Cancer Institute indicated that a total of 910 000 new cancers would be diagnosed in 1985.<sup>8</sup> For common sites the numbers predicted were: lung 144 000 (15.8%), colorectal 134 000 (14.7%), breast 119 000 (13.1%), prostate 86 000 (9.5%), head and neck 58 000 (6.4%), bladder 40 000 (4.4%), endometrium 37 000 (4.1%), and pancreas 25 000 (2.7%). These eight major malignancies would account for 70% of the total incidence of cancer and 66% of the total mortality from cancer.

The review below provides a critical summary of the current state of cytotoxic chemotherapy in the treatment of these common adult malignancies.

### SMALL CELL LUNG CANCER

Untreated small cell lung cancer is rapidly fatal, median survival being only three months in patients with limited disease and 1.5 months in patients with extensive disease.<sup>9,10</sup> Although single agent chemotherapy confers a modest survival advantage in both categories of patients, appreciable long term survival (greater than 18 months) is generally achieved only with moderately intensive combinations of cytotoxic agents such as doxorubicin, cisplatin, etoposide, vincristine, and methotrexate. Such combinations have led to a fourfold to fivefold improvement in median survival compared with survival in untreated patients and to cure in a small proportion of patients with limited disease. The expected rates of objective response to treatment are about 80-90%, with a rate of complete response of 20-25% in extensive disease and 50-60% in limited disease.<sup>9</sup>

Several studies using intensive induction chemotherapy have achieved even higher rates of complete response but at the cost of considerably greater morbidity and up to 20% induction mortality. Intensive induction regimens have therefore generally failed to improve either median or overall survival.<sup>11</sup>

Of the 5-10% of patients who achieve long term survival, more than one third will die from recurrent disease and many will suffer long term morbidity related to treatment.<sup>12,13</sup> Thus despite substantial gains over the

past 10 years the vast majority of patients continue to die from their disease and both short and long term morbidity is considerable.

Elimination of resistant cell lines after initial response to cytotoxic drugs still the main objective in current studies. However, none of the approaches to prevent this—for example, alternating cross resistant regimens, high dose induction therapy with or without autologous bone marrow transplantation, and late intensification of treatment—has yet improved therapeutic prospects.

### NON-SMALL CELL LUNG CANCER

The relative success of chemotherapy in small cell lung cancer in recent years has tended to overshadow the more common, yet intractable, problem of non-small cell lung cancer. Many combination chemotherapy regimens have been studied in non-small cell lung cancer, but data on their efficacy have been difficult to interpret because of the heterogeneity of patients with regard to prior treatment, extent of disease, general state of health, differing drug doses and schedules, and variably defined response criteria. It is therefore not surprising that response rates have often conflicted, even when investigators have used the same cytotoxic combination. In addition, initial reports of high rates of response to combination chemotherapy have often been followed by more sobering results from randomised trials showing much lower activity (with only small response rates), little benefit over single agents alone, no conclusive survival advantage, and appreciable toxicity induced by the treatment.

Adenocarcinoma and squamous cell carcinoma seem to be more chemically sensitive than the large cell histological subtype.<sup>14,15</sup> Highest response rates in adenocarcinoma have been reported with vindesine given alone.<sup>16</sup> In squamous cell carcinoma the most active regimen seems to be a combination of vindesine and cisplatin.<sup>14</sup> In nine trials in which a uniform dosage schedule for vindesine was used, however, response rates varied from 1 to 31% in five trials and were less than 10% in four.<sup>14</sup> Duration of response was typically only four to six months, and overall survival ranged from 3 to 9.0 months. In the two largest series using cisplatin response rates of 2 and 32% were achieved, though with durations of response and median survivals of only three and five months, respectively.<sup>16</sup>

Despite the profusion of pilot studies of combination regimens, few have contained a control group receiving only symptomatic treatment. I study by Woods *et al.* 103 patients with non-small cell lung cancer were randomised between chemotherapy (cisplatin 120 mg/m<sup>2</sup> and vindesine 3 mg/m<sup>2</sup>) and no chemotherapy.<sup>17</sup> Overall response rates among the patients receiving chemotherapy was 30%. Toxicity was severe and there was little, if any, impact on overall survival. Thus we still lack hard evidence that the use of cytotoxic drugs either alone or in combination improves median survival or quality of life in large, unselected series of patients with non-small cell lung cancer. Indeed, it must not necessarily be assumed that response to chemotherapy correlates with either palliation of symptoms or improved quality of life.

One consolation from these many trials has been the identification of important prognostic variables that must be taken into consideration when designing clinical trials so that either false positive or false negative interpretations are avoided. For patients with non-small cell lung cancer these include initial state of health, extent of disease, the presence or absence of weight loss, histological subtype, and a history of prior treatment for disease.<sup>18</sup>

Although it is conceivable that one or more of the currently used cytotoxic combinations is beneficial to both the quality of life and duration of survival it remains an open question whether combination chemotherapy is superior to no treatment or produces an effect independent of predetermined prognostic factors. Until new agents can be identified chemotherapy for non-small cell lung cancer should be largely considered to be experimental. New approaches should be nurtured by those with specific research talent at major cancer centres.

### COLORECTAL CANCER

#### Adjuvant chemotherapy

Despite extensive evaluation it has not been established whether adjuvant (postoperative) cytotoxic treatment improves local control and overall survival in locally advanced colorectal cancer (Dukes's stages B2 and C).<sup>19</sup> The most studied treatment regimens randomise patients between fluorouracil plus semustine (methyl CCNU), and fluorouracil plus semustine plus immunotherapy.<sup>20</sup> Although many studies have yet to be reported, several of those that have been have contained major methodological inaccuracies that preclude meaningful conclusions. It is clear, however, that no appreciable benefit on overall survival from adjuvant treatment has yet emerged.<sup>21</sup> This is not altogether surprising, considering that in



treatment of advanced colorectal cancer (see below) chemotherapy is at best only marginally effective.

Because adjuvant chemotherapy in cancer of the colon is of unproved worth its routine use in any form is difficult to justify. Instead, patients should be entered into randomised clinical trials that include a control group treated by surgery alone.

There is tentative evidence that a subset of patients with rectal cancer may benefit from postoperative (adjuvant) combination therapy with pelvic radiotherapy and fluorouracil.<sup>19</sup>

#### Advanced disease

Most trials of single drugs continue to confirm the relative chemoresistance of advanced disease. Of the single agents studied, fluorouracil is the most acceptable, with an overall response rate of 15% and only moderate toxicity.<sup>20</sup> In selected cases (for example, those with a long disease free interval or well differentiated histology), however, it may afford very effective palliation for long periods.

Combination chemotherapy has yet to be proved superior to fluorouracil alone, although high response rates have often been reported.<sup>21</sup> Kemeny *et al* suggested that better results were obtained when streptozotocin was added to the combination of semustine, vincristine, and fluorouracil (response of 34% with streptozotocin v 5% without).<sup>22</sup> The Gastrointestinal Tumour Study Group and others, however, were unable to obtain equally good results and recorded appreciable toxicity.<sup>23</sup> In addition, both of these objective response rates have been achieved with fluorouracil alone, and confirmation of these results in a randomised study of the combination and fluorouracil alone is essential before such an aggressive regimen is acceptable.

#### Hepatic metastases

Treatment of patients with colorectal liver metastases by systemic chemotherapy, infusion of drugs into the hepatic artery and portal vein, and hepatic dearterialisation has been reviewed.<sup>24,25</sup> The results in these patients are disappointing despite a wide range of therapeutic manipulations. The mean survival time from diagnosis remains fairly constant at five to nine months. There is no convincing evidence from many reports on the subject that worthwhile clinical benefit can be obtained from either single agent or combination chemotherapy in most patients.

Reports on the efficacy of infusion of fluorouracil into the hepatic artery in patients with metastatic colorectal liver disease are conflicting. Several pilot studies reported an objective response rate to chemotherapeutic infusion in excess of 50% and an increase in survival rate over that of historical control groups.<sup>26,27</sup> Lack of standardisation among the trials of the site of catheter placement, drug and dose delivered, duration of infusion, response criteria, and survival analysis preclude an adequate comparison of reported results, which vary between 12% and 90%.

To determine whether fluorouracil is superior when given intra-arterially rather than systemically the Central Oncology Group embarked on a prospective controlled clinical trial comparing these two methods in 61 patients.<sup>28</sup> Though the response rate for the intra-arterial infusion arm was slightly higher than that for the systemic arm, the difference was not significant. The intra-arterial infusion arm was associated with a greater incidence of nausea, vomiting, and diarrhoea in addition to the complications of arterial thrombosis, bleeding, and infection at the site of the catheter.

#### BREAST CANCER

##### Adjuvant chemotherapy

It is now clear that many patients with apparently localised breast cancer have micrometastatic foci well beyond the scope of local treatment.<sup>29</sup> The use of systemic cytotoxic drugs after surgery or radiotherapy, or both, has been tried in an attempt to eradicate these micrometastatic foci at their most curable stage. Such a rationale is based on the results of reliable experimental data.<sup>30</sup>

The unquestioned acceptance by many oncologists, however, that adjuvant cytotoxic drugs are a worthwhile "routine" treatment for patients with early breast cancer and nodal disease is now being seriously questioned. Although trials of adjuvant therapy in breast cancer have consistently documented prolongation of the disease free survival, of the nine largest adjuvant trials, only that from the Milan Tumour Institute has seriously suggested any prolongation of overall survival beyond that in a control (surgery only) group.<sup>31</sup> The Milan trial itself, however, has been criticised for its design and also on several statistical grounds, so that its apparent improved survival of 12% at five years may be erroneous.<sup>32</sup> Thus the most

optimistic view from well designed trials is that an improvement in free survival at five years of 10-20% may occur in selected subsets of patients with positive axillary nodes; the benefit in terms of overall survival is less.

In October 1984 representatives of almost all the organisations that conducted randomised controlled trials of adjuvant cytotoxic therapy for early breast cancer met to determine whether there was any evidence that such treatment influences patient survival. An analysis of data from controlled trials indicated that among women with early breast cancer there was a clearly significant reduction in short term mortality.<sup>33</sup> For instance, net effects of cytotoxic therapy on early mortality among all treated was a 24% reduction in "odds of death." For patients aged under 60 the reduction in odds of death was 36%.

Although these preliminary analyses achieved a high degree of statistical significance, there is some uncertainty among clinicians about the interpretation and implications of the crude statistics, specifically the "reduction in odds of death." It would obviously be misleading of clinicians to equate reduction in odds of death with reduction in mortality. In addition, whether these claimed reductions in early mortality will have long benefit awaits future confirmation.

Unfortunately, early survival figures and data on the short term reduction in absolute mortality failed to provide sufficient evidence on which to value the value of adjuvant chemotherapy. No study has yet addressed the important question of whether adjuvant treatment offers any survival benefit over reserving the same adjuvant cytotoxics for the treatment of symptomatic secondary deposits. Coburn *et al* suggested that patients who "adjuvant chemotherapy may have a significantly shorter median survival compared with previously untreated women presenting with metastatic breast cancer."<sup>34</sup>

Though a longer disease free interval may be desirable for selected patients, the distressing side effects of adjuvant cytotoxic drugs can indicate their use for this purpose in most patients. The costs of adjuvant chemotherapy include acute toxicity, psychosocial morbidity, so economic impact, and chronic morbidity and mortality related to treatment. In a study in the United Kingdom up to 30% of patients undergoing adjuvant cytotoxic therapy for early breast cancer vowed that they would not undergo the same treatment again.<sup>35</sup>

Given the above findings, it is difficult to justify the morbidity induced by treatment, and a realistic argument can be made for not routinely administering adjuvant chemotherapy outside trials conducted for clinical research. Even in such research there is no longer any justification for designing a trial without a control (surgery alone) arm, and trials that compare two or more experimental arms are to be particularly deplored if their interpretation depends on the use of historical controls.

Current studies are examining the use of more aggressive regimens, shorter and longer courses, perioperative treatment, chemoinmunotherapy, and combined chemotherapy and radiotherapy.

#### Advanced disease

Although metastatic breast cancer is moderately chemosensitive, cytotoxic treatment of advanced disease is currently in a plateau phase. A multitude of regimens combining the most active drugs (cyclophosphamide, doxorubicin, methotrexate, fluorouracil, vincristine, and prednisone) have been extensively evaluated, but few have achieved a rate of complete response greater than 20%.<sup>36</sup> In addition, no combination seems to be clearly superior to any other, and overall response rates cluster in the 40-70% range.<sup>37</sup>

Combination therapy regularly achieves higher complete and partial remission rates than single agents, but higher response rates have failed to translate into increased overall survival.<sup>38</sup> Paterson *et al* presented data suggesting that aggressive combination therapy has not substantially altered long term survival in patients with metastatic breast cancer compared with less toxic single agent regimens.<sup>39</sup> There is no doubt that survival is often increased in a small subgroup of patients with life threatening, rapidly developing metastases in lung, liver, or bone marrow. In addition, long remissions with clinically useful palliation may be achieved in many patients with metastatic breast cancer without necessarily increasing overall survival; in both instances, however, our inability to assess the degree of palliation achieved (versus toxicity related to treatment) is a major stumbling block in evaluating the true worth of the available agents.

Recent studies with the most active cytotoxic drug, doxorubicin, focused on less toxic ways of administering it.<sup>40</sup> Other studies have been of newer anthracycline derivatives—for example, mitoxantrone—which promise to increase the therapeutic ratio by reducing morbidity related to treatment.<sup>41</sup> One reasonable conclusion, however, is that without more radically effective cytotoxic drugs, or the use of biological modifiers, the present stalemate is unlikely to change much.



Cytotoxic drugs with some efficacy in metastatic prostatic cancer resistant to hormones include doxorubicin, fluorouracil, cyclophosphamide, and cisplatin, which individually have achieved overall response rates of up to 40%. Criteria defining response to treatment in prostatic cancer, however, have been difficult to agree on, as this is a disease that tends to affect predominantly bone. Several response criteria have therefore been necessary. Several combinations of drugs have been used in the treatment of disseminated prostatic cancer, but response rates and durations of response have not been clearly superior to those achieved with single agents.<sup>40-42</sup>

Torti *et al* reported a randomised study of doxorubicin versus doxorubicin plus cisplatin in patients with metastatic prostatic cancer refractory to hormones. Although both agents had some antitumour activity, no advantage was seen for the combination compared with doxorubicin alone.<sup>42</sup>

An incisive review on cytotoxic treatment of metastatic prostatic cancer by Tannock concluded that there was no evidence that any form of chemotherapy resulted in substantial prolongation of survival or improvement in quality of life.<sup>43</sup> On the contrary, chemotherapy is highly toxic, especially in patients with extensive bony metastases, and "should not be regarded as part of the standard management for prostatic cancer."<sup>44</sup>

## HEAD AND NECK CANCER

### Induction chemotherapy

Over the past few years there has been rapidly increasing interest in chemotherapy for advanced squamous cell carcinoma of the head and neck. In an effort to improve local control and to prevent or kill subclinical metastatic disease in previously untreated patients many trials of induction chemotherapy have been carried out.<sup>45</sup> Results of several pilot and uncontrolled trials have shown that advanced squamous cell carcinoma of the head and neck can be effectively debulked with high dose cytotoxic combinations given before surgery or radiotherapy, or both. Overall responses of the primary tumour and nodal metastases in the neck have consistently been in the range 75-90%, with 20-60% of patients achieving a complete response.<sup>46</sup> The most promising results have been seen with a combination of cisplatin and fluorouracil.<sup>47</sup> Response rates to such treatment are considerably higher than those obtained when the same drugs are used to treat locally advanced disease, recurrent after surgery or radiotherapy.

Randomised trials have largely failed to confirm the apparent superiority of induction chemotherapy seen in pilot studies.<sup>48-50</sup> Several have failed to show any long term benefit over single agents or over "standard" treatment with radical surgery or radiotherapy, or both, despite complete response rates of up to 35% being achieved with the induction regimens.<sup>49</sup> Furthermore, one report actually showed a decreased overall survival for patients receiving induction chemotherapy, due to toxicity related to treatment.<sup>50</sup> Slotman *et al* documented a dramatic and disturbing increase in the incidence of haematogenous metastases in "successfully" treated patients.<sup>50</sup> The high initial response rates of both primary and nodal disease were partially negated by the early development of metastases in 40% of patients, often in unusual sites.

Thus whether induction chemotherapy will be of long term benefit in terms of ultimate survival remains uncertain.

### Advanced (recurrent) disease

Results of treatment of recurrent disease after radical surgery or high dose radiotherapy, or both, are discouraging.<sup>51</sup> Randomised trials have failed to show any superiority of combination regimens over single agent regimens, and the current cytotoxic "standard" is a single agent regimen, intravenous methotrexate 25-50 mg/m<sup>2</sup> weekly.<sup>52</sup> This can be expected to yield a response rate of 25-35% for a median duration of three months. Although a similar response rate may be obtained with cisplatin alone, methotrexate is better tolerated. Increasing the dosage of methotrexate does not seem to lead to higher response rates.<sup>53</sup>

Although combination chemotherapy (especially that containing cisplatin) tends to result in slightly higher overall response rates than single agents, improvements are usually short lived, toxicity is substantial, and overall survival is not extended.

## BLADDER CANCER

Systemic chemotherapy for metastatic transitional cell bladder cancer is only modestly effective. Cisplatin has achieved an overall response rate of 30% (range 25-35%) and seems to be slightly more active than other single agents, such as methotrexate, doxorubicin, and cyclophosphamide.<sup>54</sup> The recommended dose of cisplatin is 50 to 100 mg intravenously every three to

four weeks. Any appreciable responses will occur within six weeks of start of treatment; most remissions, however, are only partial and last for four to five months.<sup>54</sup>

Combinations of the four single agents mentioned above have not been sufficiently studied to permit several general conclusions. Rates of response to combination regimens are generally slightly higher than those of single agents.<sup>54</sup> Regimens containing doxorubicin without cisplatin are effective than doxorubicin alone.<sup>55</sup> There is some evidence that cisplatin plus doxorubicin, with or without cyclophosphamide, may be more active than cisplatin alone.<sup>56</sup> However, few trials have been randomised and the varying response rates obtained with combination regimens, with responses of less than 10%, make it questionable whether combination regimens confer any appreciable benefit over cisplatin alone, especially in view of the considerable morbidity experienced by patients, generally elderly. Sternberg *et al* reported a 77% response rate with a combination of methotrexate, vincristine, doxorubicin, and cisplatin.<sup>57</sup> Despite this promising result, however, it remains unproved whether chemotherapy can reliably offer clinically useful palliation or extension of survival for the vast majority of patients with metastatic cancer.

There has been recent enthusiasm for induction chemotherapy before definitive treatment of locally advanced disease with either surgery or radiotherapy. Raghavan *et al* reported their results in 50 patients with invasive, high risk bladder cancer treated initially with cisplatin 100 mg/m<sup>2</sup> intravenously in two doses with a three week interval before definitive treatment.<sup>58</sup> Major symptomatic improvement was noted in 76% of patients and 60% had an objective response. The 12 month actuarial survival was 86% and the two year actuarial survival 80%. Although similar promising results from several pilot studies are being reported, this approach must still be regarded as experimental.

## ENDOMETRIAL CANCER

Experience with cytotoxic chemotherapy in endometrial cancer is limited because of the efficacy of surgery with or without radiotherapy and the sensitivity of the disease to progestogen. For palliation of advanced disease resistant to hormones, however, cytotoxic drugs are only modestly effective. Of the many single agents studied, doxorubicin and cisplatin seem to give the highest response rates.<sup>59</sup> Combinations of doxorubicin and cisplatin in small groups of patients have yielded conflicting response rates, varying between 33% and 82%.<sup>60-62</sup> Though some authors claim that the combination of doxorubicin and cisplatin is superior to all other regimens for advanced endometrial carcinoma,<sup>63</sup> others have found that it yields similar response rates and durations of survival to either agent used singly, but at the cost of considerable additional morbidity.<sup>60</sup>

## PANCREATIC CANCER

Despite some initial promising objective responses with cytotoxic combinations such as fluorouracil/doxorubicin/mitomycin C and streptozotocin/mitomycin C/fluorouracil recent studies continue to confirm chemoresistance of pancreatic cancer.<sup>64</sup> Neither single drugs nor combination regimens achieve complete response rates greater than 5%; and these, less than 10% last one year. In a critical review O'Connell concluded that no form of current chemotherapy has been shown to offer consistent worthwhile benefit to patients with advanced pancreatic cancer.<sup>65</sup> Chemotherapy may well be contraindicated in view of its toxicity, expense and lack of demonstrable survival advantage. Instead of new trials with currently available agents being devised, "future clinical research objectives should be directed towards developing entirely new systemic agents and treatment concepts."<sup>66</sup>

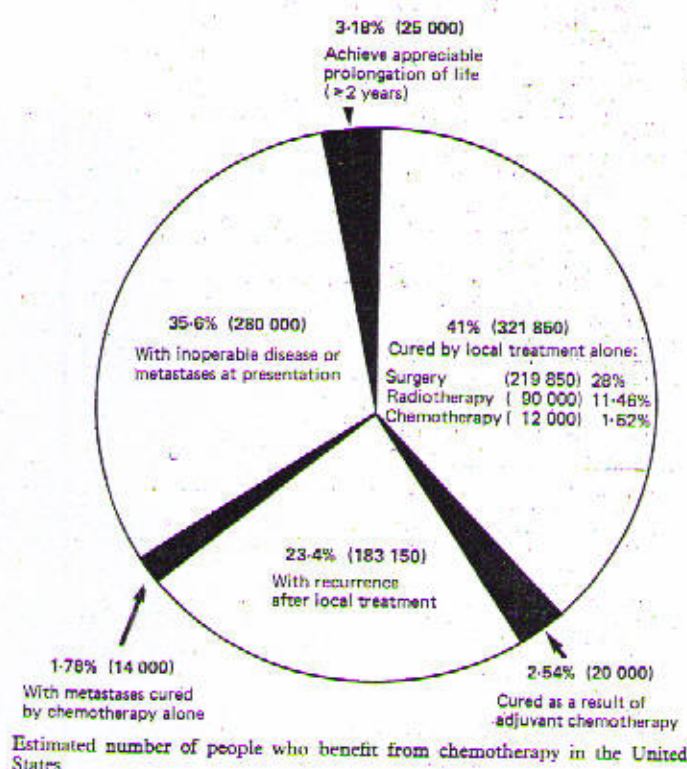
## Numerical impact of cancer chemotherapy

De Vita estimated the number of patients who benefit from chemotherapy, based on statistics from the National Cancer Institute and the American Cancer Society.<sup>1</sup> The figure shows the outcome of his assessment. In summary, 45% of all Americans with "serious" cancers will survive five years after treatment and, it is implied, will be cured. Chemotherapy will have a curative role in 5.9% of all serious (785 000) cancers and in 13.0% of all curable (356 250) cancers. In addition, 25 000 patients with incurable disease (3.2%) will experience considerable prolongation of life and 63 000 (8.0%) survival will be increased by an average of 12 months. From similar estimates made three years earlier De Vita *et al* estimated that chemotherapy was administered to over 200 000 patients in 1977, yet clinically useful effects were demonstrable in only 38 000.<sup>67</sup> "Thus," he concluded, "the majority of the patients exposed to chemotherapy will have



most of the side effects and little of the benefit.<sup>70</sup> The numerical impact of chemotherapy in adult solid tumours will be even smaller than the above estimates suggest when the influence of chemotherapy on many curable malignancies of childhood is excluded.

The popular notion that five year survival can be equated with cure is clearly of limited value because of its inability to take into account the great variations in the clinical course of different tumours. For example, carcinomas of the breast and prostate are notorious for late recurrence, occasionally well over five years after definitive local treatment. There is also controversy over how well recent improvements in five year survival rates actually reflect improved treatment.<sup>65</sup> Earlier diagnosis and treatment of cancer as a consequence of mass screening and new technology, changing diagnostic criteria, and changes in the way cancers are recorded and registered are additional important variables that have a net positive influence on survival statistics. Although dramatic advances have occurred in the treatment and survival of patients with fairly rare cancers, several eminent workers now believe that the much publicised recent gains in five year survival (and "cure") are more apparent than real.<sup>66</sup>



### Conclusions and recommendations for the future

Treatment of the most common adult tumours by cytotoxic chemotherapy is still disappointing. The current plethora of clinical papers does little to recommend the routine use of cytotoxic drugs in the treatment of non-small cell lung cancer and colorectal, prostatic, and head and neck cancers. Even in small cell lung cancer, in which cytotoxic drugs have dramatically improved median survival over that in untreated patients, toxicity is considerable and five year survival only 5-8% at best. The adjuvant use of cytotoxic drugs for "early" breast cancer remains highly contentious; for advanced disease, however, judicious use will occasionally provide long periods of clinically useful palliation. As Mead and Whitehouse recently concluded, "for most patients with advanced solid tumours, chemotherapy is not indicated as a routine practice."<sup>71</sup>

What comments and recommendations can be made for the future? Firstly, reliable criteria for assessing both tumour response and palliation (quality of life) are required. Perhaps, for instance, linear analogue self assessment scores could be incorporated into the assessment of how well stated therapeutic goals are achieved.<sup>66</sup> Improvement in these objective measures would go a long way

towards allowing non-productive, costly, and often toxic cytotoxic regimens to be recognised and discarded.

Secondly, there is a need for better designed clinical trials and a less pragmatic approach to the use of cytotoxic drugs. Controlled, randomised prospective clinical trials most definitely and accurately test new therapeutic regimens. Small, uncontrolled studies with small numbers of patients too often produce non-definitive, ambiguous results. Though phase II and pilot studies may offer clues for future treatments, their results must not be used as a basis for modifying current therapeutic successes of surgery and radiotherapy without confirmation in controlled studies. Surgery and radiotherapy still remain the only proved curative treatments for common solid malignancies in adults.

Thirdly, and a byproduct of properly conducted clinical studies, is the identification of subgroups of patients most likely to benefit from a given cytotoxic regimen. The management of advanced cancer remains a palliative exercise, and physicians need to become more sensitive to the need to tailor treatment to individual patients on the basis of factors related to both the patient and his disease.

Fourthly, we simply need newer cytotoxic agents with a more favourable therapeutic ratio. Chabner *et al* stated that "only through the discovery of significant new agents (such as interferons, lymphokines or monoclonal antibodies) will it be possible to produce durable responses and cures in the majority of patients" to eventually displace conventional cytotoxic drugs.<sup>67</sup>

Fifthly, there are lessons to be learnt by those in charge of training in oncology. Despite the disappointing performance of conventional chemotherapy in the treatment of many common solid tumours, cytotoxic drugs are being used more and more and in an uncontrolled fashion. Though such modest advances as have occurred are a stimulus for future study, they hardly justify the massive proliferation of training posts in oncology and the elevation of the specialty to "superstar" ranks, as has occurred in the United States. Medical oncologists have played, and will continue to play, an important part in basic scientific and clinical research as well as in the education of medical and lay staff. Clearly there is still a need for a limited number of pure medical oncologists to pursue basic laboratory and clinical research in large cancer centres. It would seem most cost effective, however, to train doctors to be able to work as radiotherapists as well as medical oncologists so that they may be employed to act as cancer specialists at the level of the district general hospital.

Finally, cost considerations may necessitate a more reasoned and limited approach to the use of cytotoxic drugs in the future. In a detailed analysis of the costs of cancer treatment at Peter MacCallum Hospital, Melbourne, Ilbery contrasted the high annual cost of cytotoxic chemotherapy with the considerably lower costs of megavoltage radiotherapy.<sup>68</sup> Milsted *et al* assessed the financial cost of cancer chemotherapy over 20 months during 1978-9 to be \$212 000 (or 9.3% of a major teaching hospital's total pharmacy budget for that period).<sup>69</sup> This, taken together with a median survival for patients given palliative treatment of roughly 40 weeks, led to the conclusion that "the widespread use of cancer chemotherapy is not justified outside well conducted clinical trials or specialist cancer centres." Recently, Tattersall went further in stating that "it can be argued that cancer chemotherapy should not be made available widely in the community because of its limited efficacy and significant morbidity."<sup>72</sup> I hope that the major aspects of current chemotherapy for cancer raised here will lend support to such an argument.

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*Is the natural history of Clostridium tetani such that protective levels of immunity might be maintained in those—for example, gardeners and builders—who by the nature of their work are continually suffering minor lacerations. How ubiquitous is the organism in its active and latent forms? Is there any good evidence that active immunisation should be at five rather than 10 year intervals?*

Tetanus is due to the production of toxin by *Clostridium tetani* under the anaerobic conditions present in wounds. Even those who have recovered from tetanus do not gain reliable immunity and active immunisation is therefore essential especially for those continually suffering minor lacerations that may be contaminated. The organism is widespread in soil contaminated with animal excreta (including wild animals) making, for example, football pitches a source of infection as well as domestic gardens and fields grazed by farm animals. A full basic course of adsorbed vaccine (three "primary" doses in infancy followed by a preschool and teenage booster) induces durable immunity. Following this, in Britain, it is currently recommended that further reinforcing boosters should be given after injuries but not normally more frequently than every five years, unless the wound is particularly dirty, deep, or likely to have been contaminated. Whether routine reinforcing doses are needed for adults in other circumstances is debatable but many

cases of tetanus occur without a history of preceding injury. It would seem reasonable therefore that especially those with occupational or old increased risks of infection should receive boosters at around 10 year intervals. The precise timing of boosters required to maintain protective antitoxin levels is likely to vary with individuals and it is better to be "a bit than sorry."—ERIC WALKER, lecturer in infectious diseases, Glasgow.

Joint Committee on Vaccination and Immunisation. *Immunisation against infectious disease*. London: DHSS, 1984:47-9.

## Correction

### Use and misuse of a digoxin assay service

We regret that an error occurred in this article by Dr Ian Gibb and co (13 September, p 678). In the abstract it was stated that "Treatment in 64 patients (22%) was changed either while awaiting the assay result or after receiving it. This should have read "Treatment in 64 patients (22%) was changed after assay result was received."