Modern chemotherapy in solid tumours

Successful drug treatment of solid tumours represents a considerable challenge in the mid-1990s. How effective is today's treatment, and what are the prospects for better results in the future?

Modern chemotherapy for solid tumours can be discussed in two sections: (i) its use as part of primary tumour therapy; and (ii) its use for the treatment of metastatic or advanced cancer. We begin with primary tumour therapy. 'Adjuvant' chemotherapy is a form of treatment which is given post-operatively to patients whose primary cancer has been resected, but who remain at considerable risk of relapse despite having no obvious disease spread. The best example is the use of chemotherapy in primary breast cancer. Some 20 years after the first reports of a positive benefit in randomized trials, a careful meta-analysis has clearly demonstrated that treatment given in this way leads to significant benefits in both pre- and postmenopausal women. The overall reduction in the annual rates of recurrence and of death are 28% and 16%, respectively, and it is probable that further improvements can be made by adjusting the combinations of adjuvant chemotherapy with hormone therapy.

Initial chemotherapy schedules used three drugs: cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and this is still the most widely used schedule. Current research efforts however, are beginning to identify superior schedules, for example, the initial use of adriamycin followed sequentially by CMF, which appeared to give superior results in a recent Italian trial. Many questions remain to be answered in this field. These include better methods of selecting those women who will benefit most from adjuvant treatment, and the development of more intensive forms of chemotherapy for those at the greatest risk of relapse, i.e. with multiple axillary lymph node involvement. In addition, an exciting new direction in breast cancer chemotherapy is the use of pre-operative (primary or 'neoadjuvant') treatment, which appears to be remarkably effective in shrinking tumour masses to a size whereby conservative surgery ('lumpectomy') instead of mastectomy can be carried out. There are theoretical reasons for believing that pre-operative rather than post-operative chemotherapy also carries the advantage of being more effective in reducing relapse, by preventing the emergence of resistant cells through random mutation events. Randomized trials addressing this issue should be ready for analysis in the next 1–2 years, and if positive, the use of chemotherapy in breast cancer will undergo a drastic change.

A second common cancer in which chemotherapy is likely to play an important role as part of primary treatment is colon cancer. This disease has a reputation for relative drug resistance, yet randomized trials do indicate positive benefits similar in degree to those achieved in breast cancer, particularly in patients with Duke's C cancer, i.e. those in which regional lymph-node spread adjacent to primary tumours is noted. Interestingly, these results have been obtained by combining 5-fluorouracil with the immuno-suppressive agent levamisole, and currently trials are underway to investigate whether 5-FU combined with other modulating agents, e.g. folinic acid, which has led to improved results in advanced disease, may also be more effective in the adjuvant setting. At any rate, in the USA adjuvant chemotherapy for Duke's C colon cancer is now 'standard' therapy, and time will tell as to whether and to what extent British surgeons adopt a similar policy. The priority now is the entry of as many patients as possible into prospective randomized trials, so that optimal treatment can be identified for future generations of patients with colorectal cancer.

There are other less common tumour types for which chemotherapy forms an important part of primary therapy. These include childhood and adolescent tumours, particularly Ewing's sarcoma and osteosarcoma, where pre-operative chemotherapy again plays a role in permitting conservative surgery as well as in reducing the relapse rate and improving prospects for overall survival. For a group of other tumours, e.g. cervical and bladder cancer (in which a proportion of patients present with large primary tumours and a relatively poor outlook) initial chemotherapy frequently causes considerable tumour shrinkage, and for subgroups of patients this approach is now also the subject of randomized trials.

Turning to metastatic cancer, the paradigm for a solid tumour curable with chemotherapy is testicular
cancer. This disease, which has increased in incidence by a factor of three in the past 20 years, represents the commonest form of malignancy in young men, and at initial diagnosis the majority of patients already demonstrate disease spread. Nevertheless, combination chemotherapy, which always includes cisplatin, has proved remarkably effective, with cure rates of 80–90% of patients overall. No other solid tumour carries such a high expectation of curative treatment for metastatic disease, and an understanding of the reasons which underlie the marked contrast in chemosensitivity between testicular cancer and other tumour types should be a high priority in research laboratories.

Nevertheless, chemotherapy does have a real role in improving survival in other more common forms of cancer, even when the disease is clearly metastatic. One example is small-cell lung cancer, which accounts for 25% of all lung cancer and is generally fatal when untreated within 3–4 months. Chemotherapy with a variety of agents yields responses in the majority of cases, and when the disease is of limited extent, in patients in good general condition, there is the prospect that survival can be extended by several fold, although long-term survival (>5 years) is achieved by only a small minority. Current research efforts are examining the potential for more intensive chemotherapy (in combination with radiotherapy) to improve survival.

Ovarian cancer accounts for approximately 4000 deaths per year in the UK, and because of the insidious nature of the disease, presentation in the majority of cases occurs with evidence of disease spread beyond the ovary. Nevertheless, combination chemotherapy (which includes cisplatin or its analogue, carboplatin) together with optimal ‘debulking’ surgery by a skilled gynaecological oncologist significantly prolongs survival, and again there is the prospect of long-term survival in terms of several years for a minority of cases.

For other tumour types, chemotherapy in metastatic disease is given not necessarily with the intent of prolonging survival, but with palliation as the main goal. Metastatic breast cancer is a prime example, and in many cases chemotherapy is reserved for patients who have failed prior hormone therapy. Rapidly progressive metastatic breast cancer with features such as liver or bone marrow involvement would be an indication for the more immediate use of chemotherapy and this is frequently effective in reversing the course of disease for several months.

There are other cancers which are relatively chemoresistant, especially when metastatic. These include renal cancer and melanoma, and for these diseases ‘routine’ chemotherapy should be avoided. Instead, new agents or novel forms of therapy would be legitimate treatment in such cases; this may involve developmental immunotherapy, which produces effects through the action of natural host defence mechanisms.

The range of conventional drugs used for the treatment of cancer is relatively limited. As mentioned previously, one of the key drugs is cisplatin, but the side-effects, which include nausea, vomiting, neuro- and nephrotoxicity, have to an extent limited its use. The analogue carboplatin is certainly better tolerated by patients, although myelosuppression is more common than with the parent drug, and in some tumour types cisplatin is still the preferred option. In addition, the advent of new antiemetic agents, which act by specific antagonism of the 5HT3 receptor located in the gut and in the vomiting centre in the brain, has made a substantial improvement to the tolerability of emetogenic agents such as cisplatin.

Other frequently used drugs include adriamycin, and although cardiac toxicity limits the total dose that can be given, in practice its main side-effects in addition to vomiting are alopecia and myelosuppression. Scalp cooling has provided some limited reduction in alopecia, but the greatest advances have been made recently in the amelioration of myelosuppression. Within the past few years, colony-stimulating factors have been produced through DNA recombinant technology and these do help to reduce the risk of serious infection in severely myelosuppressed patients.

For the future, a key issue is the potential importance of high-dose chemotherapy. For certain drug-sensitive cancers, it is quite possible that substantial dose increments in chemotherapy could lead to major improvements in outcome. The use of autologous bone marrow transplant has for some years allowed the use of high doses in comparative safety, specifically of those drugs for which myelosuppression is the main dose-limiting factor. However, high-dose chemotherapy has not yet been proven to give superior results to conventional dose chemotherapy, and although preliminary data in diseases such as testis cancer, lymphoma and breast cancer are encouraging, the results of current randomized trials will ultimately determine the true role of this approach.

Meanwhile, an exciting discovery has been the identification of the so called peripheral blood stem cell (PBSC). These are normal haematopoietic progenitor cells which are stimulated to proliferate in response to myelosuppressive chemotherapy in combination with the stimulus of exogenous colony-stimulating factor. Peripheral blood stem cells can be simply harvested from patients by standard leucopheresis techniques, then stored and subsequently transfused following high-dose chemotherapy. The effect is to abrogate markedly the myelosuppression resulting from high-dose treatment, and in particular...
this appears to speed platelet as well as white cell recovery.\textsuperscript{15} Studies assessing the feasibility of repeated PBSC 'mini' transplants are now ongoing, and the prospect now exists of a substantial further improvement in the results of chemotherapy when repeated high doses can be given in this way.

What other prospects are there for substantial improvements in chemotherapy of solid tumours? The limitations of currently available agents have been clear for some years and intensive efforts are being directed towards new drug development, both in the laboratory and in the clinic. Within the past year or two, one or two interesting new agents have been identified, and these look likely to be useful additions to the oncologist's armoury. These include taxol (Paclitaxel) which inhibits the depolymerization of tubulin resulting in the inability of cells to divide. The drug has attracted considerable interest, because responses have been seen in patients with ovarian and breast cancer who have become refractory to other drugs.\textsuperscript{16} The precise role of taxol in first-line treatment still has to be defined in ongoing trials, and the results are eagerly awaited, not least because of the considerable expense of this new agent, which is derived from the yew tree by a complex semi-synthetic process.

Other new drugs showing promise include inhibitors of the key nuclear enzyme, topoisomerase I (specifically analogues of a plant product—camptothecin). These agents have demonstrated activity in patients with a range of cancers, including colon cancer.\textsuperscript{17} The new agent gemcitabine is an analogue of the old drug cytosine arabinoside and it has shown activity in diseases such as lung cancer, with relatively few side-effects.\textsuperscript{18} In general, however, these new agents affect normal tissues in similar ways to established drugs, e.g. causing myelosuppression and sometimes alopecia, and more selective forms of treatment would clearly be desirable.

In this respect, in the past few years there has been an explosion of information related to the development of cancer at a molecular level. The importance of the activation of oncogenes and inactivation of tumour suppressor genes has increasingly been appreciated. The protein products of these genes may well contain clues to more selective forms for treatment of cancer, and intensive efforts are now underway both in the pharmaceutical industry and in academic institutes along these lines. Ultimately, it is hoped that rational forms of treatment which may even include pharmaceutical means for preventing development of cancer will become available over the next 5–10 years. More selective drug delivery, perhaps using genetic vectors, is an appealing prospect and one can speculate that the gene therapist will take centre stage over the next 10 years or so.\textsuperscript{19} Meanwhile, it is important to remember that improvements in the outlook for cancer patients can already be brought about by the optimal use of available resources. Expertise in cancer therapy is currently spread unevenly throughout the UK, and the speciality of medical oncology is certainly under-represented in comparison to many other countries in Europe. Cancer is the second commonest cause of death for patients in the UK, and the provision of appropriate means for its treatment should be given the priority it deserves.

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References
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