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Guest Editorial

Chemotherapy in the management of malignant disease: Current practice and future directions

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INTRODUCTION

Drugs that are able to kill mammalian cells are known as cytotoxic chemotherapeutic drugs and have been in use since the beginning of the twentieth century. They differ in their origin and chemistry, but share an ability to interfere with processes of cell division that are normally tightly regulated.

DRUG DEVELOPMENT

Chemotherapy drugs are derived from a number of sources. Some of the earliest were antifolates, chemically modified to increase their effectiveness in treating childhood leukaemias. Later developments include cytotoxic antibiotics, and more recently natural products such as derivatives of the Jamaican periwinkle *Vinca rosea* (vinca alkaloids) and the Pacific Yew *Taxus brevifolia* (paclitaxel). The explosion in molecular biology has allowed the search for new drugs to become increasingly rationalised, with the possibility of designing ideal drugs that target a particular molecule becoming a reality. We should not forget, though, that serendipity has yielded some of our most important agents. Rosenberg's chance observation in 1965 that current passing through platinum electrodes could inhibit bacterial growth led to the development of the platinum agents, starting with cisplatin.

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After active compounds are identified, development of a drug from laboratory to clinic takes around 6–10 years. The cost of development is considerable and increasing, partly because many compounds are found unsuitable or unprofitable during development. The first step answers the question of whether the drug can be given safely to humans. Following preliminary work in animals, suitable drugs enter phase I trials. In oncology these tend to recruit otherwise fit cancer patients for whom standard treatment options have come to an end, rather than the normal volunteers who might be used, for instance, in phase I trials of a new treatment for high blood pressure. Extensive blood tests are taken to examine drug handling by the body, and side effects are closely monitored. By escalating the dose until side effects become limiting, the maximum tolerated dose of drug is established.

Phase II trials ask the question 'Does this treatment work?' Using the information from earlier trials, chemotherapy regimens are tested in the clinic in specific types of cancer, usually by assessment of response such as shrinkage of tumour deposits on cross-sectional imaging. Once deemed safe and effective, drugs are licensed for use in a particular condition – in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMEA), and in the USA by the Food and Drug Administration (FDA).

It is common for drugs to be combined to maximise the response to chemotherapy. This

is thought to help by targeting the cancer cells in several different ways at the same time. Combinations are inherently more complex, with interactions among the action, metabolism and side effects of the drugs, such that some drugs simply cannot be put together in effective doses without excessive side effects. The alternative is to give the treatment in sequence. Altering drug combinations and their schedules has thus been the subject of many phase II trials.

Phase III trials are often multi-institutional, randomised comparisons of a new regimen with a current standard treatment. A placebo may sometimes be included, although this is not a common control arm in chemotherapy trials. The question often asked is 'Does treatment A help people to live longer than treatment B?' In addition, with a larger number of patients for whom the selection criteria are less narrow, more information is gathered about the likelihood of response and side effects. Positive phase III trial data are usually necessary for a treatment to become part of the 'standard treatment' in each cancer site and setting.

The final regulatory hurdle in state-run health systems is provided by advisory authorities, such as the National Institute for Health and Clinical Excellence (NICE) in England and Wales, which make recommendations about the appropriate use of treatments, based on their cost-effectiveness. These guidelines can rely heavily on specific trial results to recommend the patient group for treatment and the outline of the treatment. See Box 1 for the evolution of the NICE guidelines for colorectal cancer, incorporating the accumulating evidence for use of the newer agents oxaliplatin, irinotecan and capecitabine; further information is available from the NICE website (see useful websites section).

Cost-effectiveness is less of a driver in insurance-based systems (e.g., in the USA) and where physicians are remunerated for visits and doses of treatment. This leads to a tendency to adopt new treatments sooner and continue treatment longer.

USES FOR CHEMOTHERAPY

Early disease

In the past two decades it has become common practice to give 'adjuvant chemotherapy' after the primary cancer has been removed. For example, adjuvant chemotherapy for women who have had potentially curative surgery for breast cancer is now well established, although it was an unpalatable concept for the oncological community when Bonnadonna and colleagues first proposed and used their CMF (cyclophosphamide, methotrexate and fluorouracil) regimen in the 1970s.[1] This approach was based on the concept that chemotherapy may be able to eradicate small numbers of cells that might have metastasised from the primary cancer and settled in other organs, known as micrometastases. There is good evidence that, to achieve this goal, one has to start the target dose of a combination of agents as soon as possible after surgery and without delay in treatment. The barrier to acceptance of this concept lay in the fact that the nature of such risk-reduction strategies means that a good proportion of patients already cured by surgery will undergo unnecessary chemotherapy; furthermore, some patients will have recurrence of cancer despite the adjuvant chemotherapy. It is therefore important for the patient to understand the short-term and long-term risks associated with the treatment. To understand the potential benefit, risk calculators based on pathological information from the primary tumour are useful and now used routinely (see useful websites section). It is hoped that in the course of time, molecular analyses of the primary tumour will be available that reduce these elements of uncertainty.

Schedules where chemotherapy precedes surgery, known as neoadjuvant chemotherapy, are becoming more frequent. Table 1 shows cancer sites where the two approaches are currently used. Breast cancer is again a good example: inoperable large or inflammatory tumours can be effectively down-staged for successful surgery and allow (often visible) testing of the sensitivity of the disease to the chemotherapy regimen. Potential difficulties are associated with this approach, such as more

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Box 1. NICE Guidance on Chemotherapy for Colorectal Cancer

March 2002 NICE Technology Appraisal 33
Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer

1. Guidance

1.1 On the balance of clinical and cost-effectiveness, neither irinotecan nor oxaliplatin in combination with 5-fluorouracil and folinic acid (5FU/FA) are recommended for routine first-line therapy for advanced colorectal cancer.

1.2 Oxaliplatin should be considered for use as first-line therapy, in combination with 5FU/FA, in advanced colorectal cancer in patients with metastases that are confined solely to the liver and may become resectable ('down staged') following treatment.

August 2005 Review of Technology Appraisal 33

1. Guidance

1.1 Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced colorectal cancer as follows:

- irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
- oxaliplatin in combination with 5-fluorouracil and folinic acid as first-line or subsequent therapy.

1.2 Raltitrexed is not recommended for the treatment of patients with advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.

April 2006 NICE Technology Appraisal 100
Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer

1. Guidance

1.1 The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:

- capecitabine as monotherapy
- oxaliplatin in combination with 5-fluorouracil and folinic acid.

1.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.

challenging surgery, delayed healing and patients being less fit at the time of surgery. In addition, those patients whose disease is resistant to chemotherapy will have potentially curative surgical treatment delayed, probably to their disadvantage.

As a definitive treatment for cancer, chemotherapy and radiotherapy can be combined. It is possible to cure squamous cell carcinomas of the head and neck, anus and less commonly the oesophagus with cisplatin-based chemoradiotherapy. In this instance the drugs are acting partly as radiosensitisers, and therefore the doses used may be lower than when they are given alone. In addition, the exact timing of the chemotherapy with respect to fractions of radiotherapy can be crucial to ensure that cancer cells are at their most vulnerable to the effects of radiation. Among newer drugs, gemcitabine is promising as a radiosensitiser, particularly in the lung, where quite small doses seem to be effective.[2]

Metastatic disease

The majority of chemotherapy finds its use in the metastatic setting. Here the goals of treatment are generally to improve symptoms and sometimes to achieve a significant survival benefit, that is, to help people to live longer, and to give a greater quality of life for that time. This is also known as palliative chemotherapy.

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Table 1. *Overview of current roles for chemotherapy in early disease by primary cancer site*

	Adjuvant chemotherapy	**Neoadjuvant chemotherapy**
Breast	High-risk groups (e.g., node positive)	Large but operable; inflammatory tumours
Colorectal	High-risk groups (Duke's C and high-risk Duke's B)	Before liver metastasis resection
Lung	High-risk groups	No
Stomach	Stage II or higher (combined approach)	
Oesophagus	Not routine	High-risk groups
Pancreatic	High-risk groups	No
Head and neck	No	Emerging role before chemoradiotherapy
Brain	Increasingly	No
Ovarian	High-risk stages I–II	Not standard
Endometrial	Not standard	No
Cervical	No	No
Bladder	High-risk groups	High-risk groups
Renal	No	No
Adult sarcoma	High-risk groups	No
Testicular	High-risk groups	No
Prostate	No	No
Melanoma	No	No

The conventional measure of outcome in this setting has been the response rate to chemotherapy. Derived from phase II or III trials, this is the percentage of people treated whose disease improves by a certain benchmark. The WHO criteria, and more recently the RECIST criteria, are the two systems of measurement most commonly employed.[3,4] As a general rule, response to chemotherapy leads to improved symptoms and survival. The art of palliative treatment is to achieve a balance between the benefit from chemotherapy and its side effects, which include the inconvenience and anxiety associated with the treatment. There is often more than one choice of effective chemotherapy regimen, and the most effective tends to be preferred for initial (first-line) treatment, with those less effective regimens reserved for later if appropriate (see Table 2).[5] In chemosensitive diseases such as ovarian cancer, those who respond to first-line treatment may experience a long relapse-free interval and then respond again to the same treatment potentially on several occasions.[6] There tend to be diminishing returns in these situations.

Definition of the most effective treatment can be controversial. For instance, newer drugs may produce greater response rates in trials but may not have been shown to have an impact on survival. Often a newer drug will have less severe side effects and may have a more convenient form of administration, such as an oral formulation. Invariably, it will be many times more expensive than existing drugs, which is the *raison d'être* for bodies such as NICE, who are charged with assessing their impact on quality of life versus the cost to the health system.

Table 2. *Response rates of common first-line chemotherapies*

	Response rate (%)
Colorectal cancer	
5-fluorouracil (5FU)	10–20
Capecitabine	10–30
Mitomycin-C/5FU	15–45
Oxaliplatin/5FU	35–55
Irinotecan/5FU	30–55
	See ref. (5)
Breast cancer	
Epirubicin or doxorubicin	45
5FU/epirubicin/cyclophosphamide (FEC)	50
Epirubicin/cisplatin/5FU (ECF)	85
Docetaxel	30–65
Docetaxel/capecitabine	42

Unfortunately, the response rate for a treatment expresses only the chance of 'response' for each person in the population studied (trial population), who tend to be on average younger and fitter than the patient population referred for treatment. There are disease factors that can be helpful in predicting response, such as pathological subsets (based on microscopic

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Table 3. ECOG (Eastern Cooperative Oncology Group) performance status[9]

Grade	
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

appearance of tumour cells or their expression of certain markers) and patterns of metastatic spread. However, patient factors tend to be most important, with fitter patients responding to treatment more often and to a greater degree. Although age of the patient is a factor, palliative chemotherapy can be given with caution even to the very elderly, who, it seems, are as likely to benefit from it.[7,8] Again overall fitness is paramount. This is conventionally depicted by performance status (Table 3).[9]

The decision of whether to embark on treatment with a particular chemotherapy at a particular stage is ideally made by a fully informed patient. Clearly the difficulty with concepts of chance of response, unknown level of side effects and, ultimately, uncertainty about the outcome mean this tends to be a decision guided by the clinician.

Once a course of chemotherapy has started, a patient is supported by a network of health professionals. An important part of the development of chemotherapy services has been the shift in administration and support for chemotherapy towards specialist nursing services. The majority of treatments can be given in the outpatient clinic by experienced staff who are consistent contacts for a patient. Some regions even provide 'chemotherapy at home' services so patients can be treated in a more convenient and comfortable environment.

The patient is assessed early in a course of treatment to evaluate any problems experienced and modify treatments such as anti-emetics accordingly. Through the course of treatment, it is important to evaluate whether there is a response in terms of symptoms, signs, blood markers and definitive radiological measurements. If so, the balance of 'benefit' versus 'cost' is usually in favour of continuing treatment. However, it is never appropriate to continue potentially dangerous treatment if the cancer progresses despite treatment. If chemotherapy is helpful in stabilising or slowly shrinking metastatic disease and the side effects are manageable, treatment could feasibly continue for many months. An alternative approach – treating for a defined duration and then waiting for progression of disease before recommencing an effective regimen – is currently the subject of investigation in metastatic colorectal cancer. In the UK COIN trial, treatment with oxaliplatin combined with fluorouracil or capecitabine is randomised to be either continuous or intermittent (see MRC website). For oxaliplatin-based therapy this is of particular interest, because it often causes a disabling numbness and difficulty with the use of the fingertips with prolonged use.

SIDE EFFECTS OF CHEMOTHERAPY

The most important side effect of chemotherapies is their ability to suppress the production of blood cells by the bone marrow. This myelosuppression typically results in a fall in circulating white blood cells and platelets 1–2 weeks after a dose of treatment, with recovery by the end of the third week. Hence a majority of chemotherapy regimens incorporate three-weekly dosing of drugs. The effect varies between different regimens both in degree and in the time of lowest counts (the nadir). In solid tumour treatment, the greatest risk is from severe infection owing to lack of particular white blood cells known as neutrophils (neutropenia), which

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mediate many of the normal responses to bacterial infection. In a patient who lacks sufficient neutrophils, bacteria that otherwise would be harmless can cause overwhelming infections with rapid onset and life-threatening consequences. It is vital that all patients receiving chemotherapy know to be vigilant for signs of infection and are able to contact the hospital immediately for advice and treatment. Trials commonly report approximately 1% mortality directly attributable to chemotherapy, even in the fittest populations, mostly as a result of neutropenic infections.[10]

Dose delays and reductions may be necessary to avoid further problems from myelosuppression, which in the palliative setting is usually a reasonable step, but in curative settings could compromise the chance of cure. This can be avoided, to a degree, by employing the human neutrophil growth factor GCSF. This has been taken a step further to allow chemotherapy doses to be given at closer intervals, which is thought to increase their effectiveness. Such 'dose-dense' treatment is being evaluated in breast cancer, for example, in the UK TACT2 trial of adjuvant chemotherapy (see NCRI website).

Red blood cells have a longer lifecycle of 120 days and their number falls more slowly during a course of chemotherapy. Sometimes patients will benefit from transfusion of red cells to improve symptoms or response to treatment, or less commonly drugs related to erythropoietin can be used to stimulate red cell synthesis. The latter approach is currently under consideration by NICE.

Chemotherapeutic agents, being elegant poisons by nature, tend to cause unpleasant side effects that disturb the quality of life temporarily. Many drugs cause a degree of nausea and vomiting that can be settled with a number of drug treatments. The introduction of the 5-HT3 antagonists such as ondansetron has revolutionised the experience of patients receiving platinum-based drugs, which were previously associated with severe sickness.

Many patients experience lethargy and feel 'off colour' following each course of treatment. Otherwise hair loss, soreness of the mouth and constipation/diarrhoea are common problems. As with response to treatment, it is difficult to predict with any certainty which side effects are likely to manifest, except to say that fitter patients tend to experience fewer problems.

In the medium term, hair will grow back and fitness return; some patients, however, will be left with unpleasant tingling/numbness of the finger tips (cisplatin, oxaliplatin, paclitaxel), deafness/tinnitus (cisplatin), menopausal symptoms or infertility. Continuing improvements in reproductive medicine technologies mean that semen storage can circumvent the latter problem for some men. Counterpart treatments for female patients are less commonly available and less successful.

Thrombosis and potential lethal pulmonary embolism and heart attack (myocardial infarction) can also be consequences of chemotherapy and are aggravated by common risk factors in the cancer patient, who is often a smoker.

LONG-TERM EFFECTS

In adult solid-tumour oncology the field of late effects remains in its infancy. Particular drugs are associated with later problems, which can be relevant to adjuvant treatment, where chance of survival after treatment may be significant. The anthracyclines used in breast cancer pose a dose-dependent risk of heart muscle damage (cardiomyopathy), several drugs are associated with life-threatening lung fibrosis (bleomycin used in testicular cancers, methotrexate), and etoposide in particular (again in testicular cancers) can cause lethal leukaemias several years after treatment. More subtle changes in blood pressure, lipids and the risk of ischaemic heart disease are now being recognised, not to mention the long-term psychological and cognitive effects of chemotherapy.

THE OUTLOOK FOR CHEMOTHERAPY TREATMENTS

The uses of chemotherapeutic agents have continued to broaden in terms of cancer types

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and stages of disease since their introduction in the twentieth century. However, it has become clear that with limiting side effects and a propensity to be most useful in fitter patients, the advances still to be made will improve outcomes only to a degree or help only selected groups of patients. With the increased understanding of the biology of cancer, distinct novel therapies are becoming more widespread. It is hoped these targeted treatments will go some way to improving the benefit-to-side-effect ratio of treatments. Again, the benefits may be limited to smaller groups of patients, but can be dramatic. A case in point is the drug imatinib (Glivec, STI-571), which is able to stabilise disease in the rare gastrointestinal stromal tumour (GIST) for many months, where conventional chemotherapies are ineffective and patients previously had a dismal prognosis.[11] As with a number of similar drugs, imatinib is given orally and has relatively minor side effects. Its cost, however, is approximately £20,000 per year. In other cases, new therapies are combined or sequenced with conventional chemotherapy; examples include antibodies such as trastuzumab (Herceptin), cetuximab (Erbitux) and bevacizumab (Avastin) in subgroups of breast and bowel cancers. Currently less than a quarter of new cancer drugs in development are cytotoxic.

As information grows about the benefits of chemotherapy, it is already possible to see how identifying more pathological/molecular characteristics of the tumour and defining the stage of disease closely can affect the treatment given. Improvements in both pathology and radiological investigations, and particularly their discussion at multidisciplinary meetings (MDTs), should lead to the best use of the available treatments. In addition, the NHS Cancer Plan has galvanised improvement in the supportive medical, nursing, social and psychological care of patients receiving chemotherapy (see Department of Health website).

CONCLUSIONS

Greater understanding of the mechanisms of action of cytotoxic agents at a cell and molecular level has led to some improvements and refinements of the drugs available for use in the clinic today, and an increase in the sophistication of strategies used to combat cancer (e.g., the concept of 'adjuvant' treatment). Nevertheless, with the exception of testicular cancers and haematological malignancies, there are few adult tumours for which developments in chemotherapy have dramatically improved rates of cure. Chemotherapies can, however, offer meaningful control of symptoms and quality of life benefits in advanced disease. Improved side effect profiles of newer agents and better supportive medications such as anti-emetics have made this more achievable.

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References

1 Bonadonna G, Valagussa P. Systemic therapy in resectable breast cancer. Hematol Oncol Clin North Am 1989;3: 727–742.

2 Wilson GD, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. Semin Radiat Oncol 2006;16:2–9.

3 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47: 207–214.

4 Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.

5 Louvet C, de Gramont A, Tournigand C, Artru P, Maindrault-Goebel F, Krulik M. Correlation between progression free survival and response rate in patients with metastatic colorectal carcinoma. Cancer 2001;91:2033–2038.

6 Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 1990;36:207–211.

7 The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 1999;91: 66–72.

8 Maione P, Perrone F, Gallo C et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 2005;23:6865–6872.

9 Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.

10 Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905–914.

11 Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–480.

USEFUL WEBSITES

Drug regulatory/government bodies

MHRA: www.mhra.gov.uk

EMEA: www.emea.eu.int

NICE: www.nice.org.uk

Department of Health: www.dh.gov.uk

Risk calculator for breast and bowel cancer recurrence

www.adjuvantonline.com

Clinical trials bodies

MRC: www.ctu.mrc.ac.uk

NCRI: www.ncri.org.uk

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