Reviews in Medicine

Oncology

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Introduction

In looking at the 2 years since the last review it is apparent that there is no slowing in the pace of discovery and innovation in the scientific aspects of oncology, and the application of these ideas in the clinic. Once again, the aim is to help the general physician with practical information, and while some topics have been updated, a number of new ones have been introduced.

Molecular oncology

At its simplest, it could be said that the molecular biology of cancer suggests that genomic changes encompass the altered expression of two classes of gene directly concerned with cancer: firstly, those genes whose encoded protein increases oncogenic potential (the so-called oncogenes), and secondly, those genes that decrease or inhibit the activity of oncogenes (known as tumour suppressor genes). The latter can be defined as genes where the loss of function is oncogenic. By restoring the suppressor gene, it can be shown that oncogenesis can be prevented. The role of the suppressor gene is best illustrated in retinoblastoma,¹ where an allelic deletion is seen on chromosome 13 in the q14 region. As long as the retinoblastoma suppressor gene (RB) is retained on one allele, then the tumour will not develop; loss of both genes results in tumour induction. Initial loss, of course, may be an inherited mutation, but the second loss is somatic. It has been shown that the RB gene produces a DNA binding nuclear protein which has the ability to form protein–protein complexes with DNA tumour virus oncoproteins.² The dephosphorylated form of this protein is now identified as the active tumour suppressor.³ This rare tumour therefore provides an example of how malignant change can originate, but is this any more than a curiosity?

In studying lung cancer Minna⁴ has shown that, unlike retinoblastoma, multiple mutations in the cell are needed before a tumour such as small cell lung cancer develops, and this is true of other adult solid tumours such as colon cancer.⁵ The most prominent cytogenetic abnormality in small cell lung cancer is a deletion or unbalanced translocation on the short arm of chromosome 3 (3p), which occurs in 90% of cases; but non-random abnormalities are also noted on the regions of 13q (the region of the RB gene), and 17p (the region of the p53 gene).

Both chromosome 17p and chromosome 3 bear further examination in the light of recent discoveries. The term 'Li Fraumeni syndrome' is used to describe a familial association between maternal breast cancer and soft tissue sarcoma in children. First described in 1969,⁶ it now comprises some 200 families who have been shown to have an excess of rhabdomyosarcoma, glioblastoma, breast cancer, leukaemia and adrenocortical tumours. Malkin,⁷ has investigated five families, examining members of the p53 gene. In every family, a germline mutation of this suppressor gene has been discovered, providing convincing proof that p53 is concerned with growth control. Like the RB gene, the p53 gene produces a protein that complexes with the DNA tumour virus and undergoes the same cycle of phosphorylation and dephosphorylation. Recent studies have shown that the p53 gene is the one most frequently mutated or lost in virtually every solid tumour so far tested.

It seems unlikely as yet that this knowledge can be put to practical use, but in the other gene mutations mentioned, on chromosome 3, there may perhaps be an opportunity. Minna has found frequent deletions or translocations involving the short arm of chromosome 3, not only in small cell lung cancer, but also in non-small cell lung cancer. Among the candidate recessive oncogenes on this chromosome is the retinoic acid receptor gene and, as will now be shown, this may have a significant influence on the stepwise progression towards malignancy in a cell.

The prevention of cancer

A major goal must be to prevent cancer, particularly those cancers that are common or unresponsive to treatment. In addition to the well-studied relationship between smoking and various cancers, two new fields of investigation have recently been opened. The first is the use of retinoids in the prevention of disease of the gastrointestinal and respiratory tracts, and also in the prevention of recurrence of epitheliomatous tumours such as cancer of the head and neck, breast cancer and the childhood neuroendocrine cancer, neuroblastoma.

The concept of multi-step carcinogenesis strongly indicates that all parts of the respiratory epithelium are liable to develop malignancy in this manner. Retinoids have been shown to suppress this process. Hong *et al.*⁸ showed that 13-*cis*-retinoic acid in a randomized placebo-controlled trial prevented the development of malignant change in oral leukoplakia. Kraemer *et al.*⁹ showed that retinoids could reduce the incidence of skin cancer in the rare condition of xeroderma pigmentosum.

Further details of an adjuvant trial in head and neck cancer were given by Hong and Lippman in 1992.¹⁰ They studied the occurrence of second primary tumours in patients with cancers of the aerodigestive tract, using 13-*cRA*. Patients were stratified by tumour site and prior local treatment, and randomly assigned to receive either 13 *cRA* 50–100 mg/m²/day or placebo for 12 months. A total of 103 patients were registered, and the two groups were equivalent in all respects. At a median follow-up of 42 months the difference in the second primary tumour rate was highly significant, with only 6% of patients in the 13 *cRA* group developing malignancy, whilst 28% of the placebo group did so ($P = 0.005$). However, mucocutaneous toxicity was appreciable, and a new trial using lower doses has begun. Studies are now in progress in the United States and Europe, investigating the effect of long-term administration of retinoids in the prevention of lung cancer, second primary breast cancer, and relapse of neuroblastoma. The results of the breast cancer study in Milan are awaited shortly.

Tamoxifen and breast cancer

The incidence of breast cancer in one out of 14 of women in Great Britain makes it an important subject for studies on prevention. Until recently this has seemed an unlikely prospect. The experience gained with tamoxifen, a triphenylethylene compound with anti-oestrogenic and oestrogenic properties, that causes breast cancer cells to accumulate in G0 and G1 of the cell cycle, and to stop growing, has resulted in its becoming a

candidate agent for chemo-prevention.

The Early Breast Cancer Trial Collaborative Group report¹¹ has shown that there is a 25% reduction in the risk of relapse at 10 year follow-up. Cusick and Baum,¹² reporting the results of a Cancer Research Campaign trial, showed a reduction in contralateral primary breast cancer, and this was confirmed in the world overview.

Tamoxifen is relatively free of side effects. The major symptoms are those of oestrogen withdrawal. Concern had been expressed at the possibility of a deleterious effect on lipid and mineral metabolism, leading to long-term complications. However, in these studies it has become apparent that these long-term side effects are absent, and indeed, there is some indication that the incidence of ischaemic heart disease and osteoporosis may be diminished.

Given the undoubted efficacy, how should a trial be conducted? It would be easier if there were plentiful numbers of women at high risk, with risk factors that could be clearly defined, but only about a quarter fall into this category. For ethical, logistic and financial reasons it is not possible to include all women. Pilot studies¹³ have helped to address some of these problems. Trials have now started in the United States and Great Britain, where it has been decided to include women in the peri- and post-menopausal age of life, with a two-fold risk or more of developing breast cancer. They will be treated with 20 mg of tamoxifen daily for 5 years.

Short-term and long-term toxicities of anti-cancer therapy

Nausea and vomiting are among the most unpleasant of the short-term toxic effects of chemotherapy, and cardiac damage is emerging as a serious long-term effect, particularly after anthracycline drug administration.

Most oncologists would agree that the 5HT₃ (5-hydroxytryptamine₃) inhibitors have revolutionized their practice over the last year or so. The precise mechanism of action is not known. Chemotherapeutic agents probably release 5HT in the small intestine, which initiates a vomiting reflex via the 5HT₃ receptors. GR38032F (ondansetron) is a highly selective 5HT₃ receptor antagonist blocking both peripheral and central receptors, and is evidently the first of a series of similar compounds. They have strikingly few side effects, and sedation or extrapyramidal complications have not been noted. They are particularly effective against nausea and vomiting induced by platinum compounds¹⁴ or high-dose melphalan.¹⁵ Viner *et al.*¹⁵ reported that in 42% of patients treated with high-dose melphalan (140–200 mg/m² intravenously (i.v.)) emetic episodes were either abolished (15%) or reduced to only two (27%). Two dose ranges were

studied, and in one patient where control was not achieved, ondansetron levels were within the effective range, so that it seems that patients can fail on standard doses. It is recommended, therefore, that the dose is titrated to the likely emetogenic effects of the agent used. A dose of 8 mg given either by slow intravenous injection or a 15 minute infusion should be started before chemotherapy is given. If given orally, the dose of 8 mg should be administered 1–2 hours before chemotherapy. It is compatible with cisplatin, carboplatin, fluorouracil, etoposide and cyclophosphamide, and can be infused simultaneously at specified concentrations if symptoms indicate the need for further drug administration. The possibility that dexamethasone may enhance the anti-emetic effect, and help in those few patients who are not responsive to 5HT₃ inhibitors was studied in a trial by Smith *et al.*¹⁶ They randomized patients to ondansetron and dexamethasone, or ondansetron and placebo. Patients were receiving high-dose cisplatin therapy, and it would be expected that nausea and vomiting would be controlled in some 40–60% by ondansetron alone. Dexamethasone was given at 8 mg orally, 8 hourly. Ondansetron was given a 8 mg orally every 8 hours for the 8 days of the intensive therapy. Elimination of vomiting, or reduction in emesis, was highly significant in the ondansetron plus dexamethasone group ($P < 0.001$ by the end of the 8 days).

The disadvantage of the high cost of 5HT₃ inhibition has to be set against its effectiveness in controlling this often intolerable side effect, allowing the treatment programmes to be completed, and reducing the necessity for in-patient admission. The careful use of 5HT₃ inhibitors is probably cost-effective.

Late cardiotoxicity of anthracycline drugs

A disturbing late toxic effect of chemotherapy regimens which have included anthracyclines is the occurrence of sudden death in young people when subjected to cardiovascular stress. Death has occurred on exercise or parturition, and a feature of these patients has been the use of anthracycline as treatment for their cancer in childhood.

The cardiotoxic properties of anthracyclines have been known since the early 1970s.^{17,18} The toxicity is due to damage of myoblasts in the myocardium, and since myoblast formation is complete by 9 months, and replacement does not occur after that time, cardiotoxic drugs given to children, especially young children, can prejudice normal cardiac development, leaving the patient with what appears to be a normal heart, but one in which the ventricular muscle is reduced in thickness, so that the cardiac reserve is impaired. Few studies had been done on the long-term effects of

anthracyclines until last year, when a number of reports on assessment of cardiac function some years after treatment have appeared, and although there are some discrepancies, the message that long-term damage does occur is clear.

One of the most extensive studies was an investigation of the cardiac status of 115 children who had been treated with doxorubicin for acute lymphoblastic leukaemia 1–15 years earlier.¹⁹ The children had received from 228 to 550 mg/m², and the median time for evaluation was 6.4 years after administration of the dose. Evaluation consisted of a history, 24 hour electrocardiogram, exercise testing, echocardiography and determination of various parameters of cardiac activity. Details are shown in Table I.

Using conventional criteria such as contractility, these authors showed that 65% of children receiving more than 228 mg/m² of doxorubicin had increased afterloading, or decreased contractility, or both, and that the thickness of the left ventricular wall was diminished. They showed that the effect was related to total cumulative dose of doxorubicin, and was more severe in young children. Their studies were compatible with the hypothesis that myocytes are lost from the developing heart as a result of doxorubicin administration.

This is a disturbingly high level of impairment. Smaller studies, such as those by Yeung *et al.*²⁰ in Australian children, again confirm late cardiac effects in 19 children selected from a series of 263 long-term survivors who had had anthracyclines. In a further 10 selected children who had not had anthracycline, no cardiac abnormalities were seen. It would seem important to reassess cardiac status in adolescents and young patients who have been treated with anthracyclines as children, and whenever possible, to limit the dose of doxorubicin and daunorubicin in proposed new trials of treatment for acute leukaemia and solid tumours, particularly where very young children are to be admitted to these protocols.

These findings enhance the value of agents that are able to protect the heart. The possibility that doxorubicin's cardiomyopathy might be prevented by dextrazoxane ADR 529 (ICRF 187) has been suggested for some time. Dextrazoxane (DZR) is an intracellular chelator which binds iron after it forms complexes with doxorubicin, thus preventing the formation of free radicals which damage the myocyte.

Rosenfeld *et al.*²¹ reported a study of women with breast cancer, who had not previously received anthracyclines, but were now being treated for advanced breast cancer with drug programmes including anthracyclines; 50% received 500 mg/m² of DZR and 50% a placebo. Of 349 patients who were evaluable, 181 received the blinded placebo. After 600 mg/m² cumulative dose of doxorubicin,

Table I Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukaemia in childhood. Contractility determined by fractional shortening, velocity of shortening and left ventricular end systolic wall stress

Characteristic	No. of patients	Cardiac abnormality		
		Any abnormality	Increased afterload	Decreased contractility
Total doxorubicin (mg/m ²)				
45	18	3 (17%)	3 (17%)	0 (0%)
228–360	52	29 (56%)	26 (50%)	7 (13%)
361–477	42	31 (74%)	28 (67%)	12 (29%)
>500	3	3 (100%)	3 (100%)	3 (100%)
228–550	97	63 (65%)	57 (59%)	22 (23%)

Adapted from information which appeared in Lipshultz, S.E., Colan, S.D., Gelber, R.H. *et al.* Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukaemia in childhood. *N Engl J Med* 1991, **324**: 808–815.

17 remained on treatment in the DZR group, and only eight in the placebo arm. Patients in the control arm had a 2.5 times greater risk of developing a cardiac event, and a beneficial effect was noted when 400 mg/m² cumulative dose of doxorubicin was achieved. At this level, controls had a 10-fold risk of developing congestive cardiac failure, which was significant (*P* < 0.005). This would suggest that there is short-term protection against the effects of doxorubicin, and by implication one may hope that this would translate into long-term absence of cardiotoxicity. Further randomized studies, with longer follow-up, are certainly needed.

New drug development

It has been a feature of the interval since the last review of therapy was written that a significant number of new anti-cancer agents, and notably new chemotherapeutic drugs, are becoming available for clinical use. A selection has had to be made, and drugs which are not analogues of established agents, or which have activity in hitherto unresponsive tumours, have been selected.

Gemcitabine

Difluorodeoxycytidine (Gemcitabine, dFdC) is a new anti-tumour anti-metabolite entering Phase II clinical trials. Biochemically dFdC is metabolized to dFdCTP. This anabolite has a very long intracellular half-life, which may account for its encouraging activity in Phase I trials. It is one of the first anti-metabolites to be shown to be active against solid tumours. A particularly interesting aspect of its activity is that it has produced responses in

non-small cell lung cancer without intolerable side effects. This is a tumour which most physicians have preferred not to treat with chemotherapy, since the response rate and effect on quality of life was so poor for most of the regimens proposed. A recent study,²² treating non-small cell lung cancer by Gemcitabine (800 mg/m² i.v. weekly for 3 weeks, followed by a week's interval of no treatment), has suggested a well-tolerated regimen, the only problem being some mild nausea and vomiting, occasional 'flu-like syndrome immediately after administration, and lethargy. Some patients had had mild myelosuppression, 1% with grade 3 World Health Organization impairment, but the myelosuppression was manageable, and on the whole did not need blood product support. In this interim report, 36 patients with measurable disease had been treated and, of these, seven independently validated, partial responses had been shown to occur, in a tumour notoriously unresponsive to chemotherapy, and these had been for a significant period of more than 5 months. If these responses can be confirmed, and shown to be achievable with a satisfactory quality of life, then it is possible that this new agent may have a role in the management of non-small cell lung cancer.

Gemcitabine is now being studied for its effect on gastrointestinal cancer. American series have reported responses. In pancreatic cancer,²³ 43 patients who had had no previous chemotherapy were treated with doses of 800 mg/m² i.v. weekly for 3 weeks every 28 days, the doses escalating to a total of 1,250 mg/m² weekly. Five of 39 evaluable patients showed a >50% decrease in the size of the tumour lasting for between 3 and 9 months. These results must be treated with caution, in view of the difficulty of assessing response in pancreatic cancer, but again, further investigation would seem

justifiable. Smaller studies in colon cancer²⁴ have not yet shown any evidence of response.

2-Chlorodeoxyadenosine (2-CDA)

Another new anti-tumour anti-metabolite recently introduced for clinical evaluation is 2-chlorodeoxyadenosine (2-CDA). This is active against resting and dividing cells of the lymphoid series. Its mechanism of action requires phosphorylation by deoxycytidine kinase, an enzyme expressed mainly in lymphoid tissue. 2-CDA produces responses in both high-grade and low-grade lymphoid malignancy. It also shows activity against myeloid cells.

Its outstanding success has been in the treatment of the rare hairy cell leukaemia (HCL).²⁵ More than 75% of patients with HCL achieved complete remissions, and none have relapsed. It is likely that 2-CDA will be the drug of choice in this condition. In a study of low-grade intermediate and transformed lymphoma, a 50% overall response rate was noted.²⁶ Those who did not respond had usually been heavily pretreated with other anti-lymphoma therapy. In this study, the three patients who achieved a complete response had low-grade non-Hodgkin lymphoma.

In myeloid malignancy, there is a report of complete haematological remissions in all five patients with chronic myeloid leukaemia,²⁷ where the peripheral leucocyte count returned to normal, the platelet count recovered, and there was complete resolution of splenomegaly. At the time of reporting these five patients, the longest had been in remission for 6 months. None of them had suffered any toxicity.

It is evident that naturally occurring substances with marked anti-cancer properties are being found from time to time. Two of the most interesting are a vitamin (retinoic acid), and a plant product (taxol), and these have been the subject of extensive comment in both the professional and the lay press. The definition of the clinical role of these two substances is still under scrutiny, but the fact that work is being done emphasizes how much we need to continue our examination of naturally occurring substances, and to preserve as far as possible their sources.

Retinoic acid

Huang *et al.*²⁸ first showed that the isomer ALL-trans retinoic acid produced complete remissions in acute promyelomonocytic leukaemia (APML), which is classified as M3 in the French-American-British (FAB) classification of acute myeloid leukaemia. This leukaemia forms from 5–15% of all acute non-lymphoblastic leukaemias, and is notable for its coagulation disorder, which produces a problem for remission induction, many

patients dying from haemorrhage during the early stage of the disease. However, should patients be brought into complete remission, their overall survival rate is considerably better than in other forms of myeloblastic leukaemia. A more recent finding has been the association of a non-random translocation between the 15 and 17 chromosomes in this form of leukaemia (Figure 1). Because he had limited resources in Shanghai, Huang undertook to study the use of the retinoic acid derivative in this condition, rather than using chemotherapy. In this first study he was able to report 23 complete remissions in patients with APML.²⁸ Subsequently,²⁹ in 22 patients (four of whom had been previously untreated, and 18 given conventional chemotherapy) given ALL-trans retinoic acid in a dose of 45 mg/m²/day for 90 days, two of the previously untreated group and 10 of the conventionally treated group achieved complete remissions. No patient developed problems with coagulopathy, and early deaths were due to respiratory and cardiac problems resulting from the hyperleucocytosis seen in the very elderly patients. These extraordinary results appear to be due to a specific and consistent differentiating effect on APML cells by the ALL-trans retinoic acid, rather than to a cytotoxic effect.

It has also been shown that the specific 15;17 translocation in the promyelocytic cells disappears during the induction of complete remission. When therapy is stopped, relapse occurs, and the translocation reappears. In a large study,³⁰ 180 patients with APML were treated with ALL-trans retinoic acid, and in 44 for whom there was sufficient data, a complete response was observed in 22 (50%), and in 71% of the complete evaluable patients. One partial response was seen, and eight patients had minor responses or stable disease. The drug was well tolerated, and toxicity was generally that expected with retinoids, that is, headaches, skin changes, nausea, elevation of blood triglycerides and transaminase. The syndrome of fever respira-

Figure 1 t(15;17) demonstrated by chromosome painting with a chromosome 17 paint.

tory distress, peripheral oedema and hypotension, which is occasionally seen with leucocytosis, may have been responsible for three early deaths in this study.

It is evident that the translocation 15;17 perturbs the metabolism of retinoic acid, and the administration of these large quantities of ALL-trans retinoic acid restores the growth inhibiting potential. The precise mechanism is still not understood, but it has been shown that the retinoic acid receptor (RAR) gene is localized to chromosome 17q 21.1, which is in close proximity to the non-random breakpoint t(15;17)(q22;q21). When the translocation occurs, the RAR gene is brought into close association with the *myl* gene on chromosome 15, and since the RAR gene is known to regulate expression of genes, it is possible that this gene produces a product which stimulates myeloid proliferation. In some way at present unknown, the administration of retinoic acid can inhibit this.

Despite the frequency of response to retinoic acid relapse is the rule. This was thought at first to be due to a change in sensitivity of the cells. It can be shown³¹ that cell sensitivity does not change, and there is no change in the expression of the gene hybrid; but surprisingly, plasma levels of retinoic acid fall to a level where the inhibiting activity disappears. Further work is needed to investigate this exciting story.

In practical terms it is possibly too soon to abandon the standard chemotherapeutic management of APML in the younger patient, but ALL-trans retinoic acid does provide a useful option for the treatment of the elderly patient or patients who have relapsed with the condition. However, most patients treated with retinoic acid alone relapse, unless given chemotherapy. An extensive review of this interesting topic has been published recently.³²

Taxol

This is a new substance which has shown activity against solid tumours, and has become prominent in the popular press. The material is derived from a crude extract of the bark of the Pacific yew. Its active principle contains a taxol ring, and it is an anti-microtubular agent, such as the vinca alkaloids, colchicines, and podophyllins. There are, however, important differences, because taxol induces excessively stable, non-functioning microtubules, so that other functions of the cells besides division are affected.

Phase I studies were hampered by hypersensitivity reactions, and in particular cardiac arrhythmias, neurotoxicity and neutropenia. By modifying the doses and rates of administration, it was found that a 6 hour infusion was the best way to administer the drug safely. In heavily pretreated patients with ovarian cancer, response rates of the

order of 30% were seen.³³ These responses occurred even in patients previously treated with cisplatin, and were not accompanied by unacceptable neuro- or cardiotoxicity.

Studies on taxol in other malignancies are now being reported, for example, in lung cancer and breast cancer. Five partial responses were seen in 24 evaluable patients with Stage IV non-small cell lung cancer, two lasting more than 6 months.³⁴ In another study on non-small cell lung cancer,³⁵ one patient had a complete response and five patients durable partial responses.

Review of chemotherapeutic management in selected malignancies

Non-Hodgkin lymphoma

Among the outstanding revisions of our concept of therapy in non-Hodgkin lymphoma (NHL) has been the revelation that in this condition, at least, more is not necessarily better.³⁶ In a massive study, 1,138 patients with bulky Stage II, Stage III or Stage IV intermediate or high-grade NHL were randomized to receive CHOP or one of the third generation chemotherapy regimens such as M-BACOD, ProMACE-CytaBOM, or MACOP-B. Each of these regimens was administered exactly as described by their authors. The groups of patients treated were comparable, and after a median follow-up of nearly 3 years there is no difference in response rate, time to treatment failure, or overall survival between CHOP and the third generation regimens. If subsequent follow-up confirms these results, it will provide a good argument for abandoning these programmes, which in general result in more toxic deaths, and are more expensive and difficult to administer.

In another B cell malignancy, multiple myeloma, two studies^{37,38} showed either no benefit for multi-drug chemotherapy, or a better outcome for those patients who received standard melphalan and prednisolone, compared to multi-drug chemotherapy. On the other hand, a recent MRC study³⁹ suggested that a combination chemotherapy programme was better than melphalan alone. This continuing vexed problem was reviewed,⁴⁰ and in a meta-analysis it appears that there is no advantage for multi-drug therapy compared with standard melphalan and prednisolone regimens. Where a significant improvement occurred with one or other regimen, this was largely due to the prognostic status of patients accrued to the trial. It must be hoped now that these findings will result in a re-examination of the therapeutic trials proposed in myeloma.

Lung cancer

The current management of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) remains unsatisfactory. With the exception of those patients with NSCLC who have resectable disease, the outlook remains dismal. Pre- and post-operative radiotherapy has been the subject of trials that have shown no benefit in terms of survival. Trials in which radiotherapy and chemotherapy have been combined have unfortunately been too small to give a definite answer, but it is probable that benefit, at best, has been small. Nevertheless, the possibility that new agents such as gemcitabine may produce responses is a beginning, in what has hitherto been a bleak situation.

Small cell lung cancer has shown response both to chemotherapy and radiotherapy. Chemotherapy using single agents such as etoposide has been found tolerable and particularly helpful in patients with extensive disease treated on an outpatient basis.⁴¹ Combinations such as cyclophosphamide, vincristine and doxorubicin, or cisplatin and etoposide, have been shown in some studies, and in some stages of disease, to result in complete and partial responses of over 60%.⁴² Unfortunately, this has not so far been translated into an improvement in survival, compared with less intensive single agent regimens, and has not benefited patients' quality of life.

Breast cancer

One of the most important developments in the management of early breast cancer has been the proof that adjuvant chemotherapy does delay relapse. The meta-analysis technique used by the Early Breast Cancer Trials Group⁴³ removes the inconsistencies produced by relatively small numbers, different adjuvant chemotherapy programmes, and patient accrual. Using the technique and examining the results of 133 randomized trials involving 31,000 recurrences and 24,000 deaths in a total of 75,000 patients, it was shown that either endocrine therapy or chemotherapy reduces the annual odds of death by 25%, and that 10 years after diagnosis there is approximately a 10% reduction in deaths. This analysis shows that the number of lives saved is in fact substantial. Chemotherapy was helpful in women under 50, while tamoxifen benefited the over 50s. With chemotherapy, other important findings were that prolonged treatment was better than perioperative treatment, and that multi-drug therapy was better than single agents. There was apparently no benefit in prolonging chemotherapy beyond 6 months.

The beneficial effects of tamoxifen, and the failure to confirm the suggestion that it might have deleterious effects on mineral or lipid metabolism,

make it an ideal agent for use in elderly women. There is no doubt, however, that none of the current adjuvant regimens is satisfactory, and now that the first generation methods have been confirmed as beneficial, there is a real need to develop more effective and less toxic regimens.

Ovarian cancer

Ovarian cancer was one of the first solid malignancies to show response to chemotherapy. Single agent chemotherapy, multi-agent therapy, and more recently, the platinum compounds, have been used in a number of trials which individually have failed to show convincing evidence of benefit for one regimen *versus* another. As with breast cancer, the possibility of using the overview technique has enabled the Advanced Ovarian Trialists Group⁴⁴ to examine various approaches to therapy. In comparing single non-platinum agents *versus* non-platinum combinations, the results of trials involving over 3,000 patients showed no advantage for either form of therapy. When single non-platinum agents were compared with platinum-containing combinations, there was again no difference. However, when doses of platinum <50 mg/m² were added to a combination and compared to platinum alone, there appeared to be a benefit for the platinum combinations, with a reduction of the death rate by about 15%. Platinum in the form of carboplatin was no more successful than cisplatin. It would seem, therefore, that platinum compounds are helpful, and may be used with advantage in combinations. The field is still wide open for further trials of innovative therapies in this area.

Colon cancer

After many years in which 5-fluorouracil (5-FU) has been the mainstay of palliative treatment for metastatic disease, and disappointing results have been achieved in an adjuvant setting, new methods of utilizing 5-FU, and more effective combinations of 5-FU and other drugs have become available and are now being subjected to clinical trial. A large randomized study for co-operative groups in the United States⁴⁵ reported that adjuvant therapy combining 5-FU and levamisole (an anti-helminthic) improved survival in Stage C carcinoma of the colon when given following surgery. A total of 315 eligible patients were randomized to surgery, 310 to levamisole 150 mg daily for 3 days every 2 weeks, and 304 to levamisole at the same dose plus 5-FU 450 mg/m² daily for 5 days and then weekly. Median follow-up was reported as 5 years. At this stage, deaths for the three groups were 153, 144 and 108, respectively. Levamisole together with 5-FU has reduced the recurrence rate significantly, by

39% ($P = 0.0001$). The therapy is tolerable, with no detectable long-term effects. It now seems reasonable to employ this form of adjuvant therapy for patients in this situation.

There would also seem to be a genuine advance in chemotherapy for overt colonic disease. Successful modulations of the thymidilate pool and hence cell division can be achieved by combining 5-FU and leucovorin in a carefully timed fashion. The first to report the value of this combination⁴⁶ emphasized the improved response rate, and subsequent studies⁴⁷ have confirmed that approximately double the rate of response to the combination is now being seen. The regimen is exceptionally well tolerated, and can be given on a day-patient basis. Randomized studies comparing response rates, duration of survival and performance status between the combination and 5-FU alone are now under way.

Gastric cancer

The chemotherapy of gastric cancer has been so disappointing that most randomized trials have contained a 'no treatment' arm in the randomization. Recently it has been shown⁴⁸ that a combination of epirubicin, cisplatin and 5-fluorouracil (ECF) has resulted in a substantial increase in the number of responses seen. In this study 38 patients with previously untreated adenocarcinoma of the stomach were treated with 21 weeks of 5-FU given by continuous infusion through a central line at 200 mg/m²/24 hours, combined with cisplatin 60 mg/m² i.v. and epirubicin 50 mg/m² i.v. beginning on day 1, and repeated every 3 weeks for eight courses. Seven patients had local advanced disease, 15 had local disease and liver metastases, and four had locally advanced disease and local nodes. Three patients achieved a complete response, and 28 a partial response, producing an overall response rate of 82%. All patients felt better, and toxicity was very tolerable. This programme of therapy needs confirmation and investigation on an extended scale. If these results are confirmed, the programme would be a candidate for adjuvant therapy.

Quality of life: alternative regimens in cancer therapy

With the continued failure to achieve really significant improvement in the cure rates for common cancers, particularly when they present in the more advanced form, patients, especially the well educated, are turning to alternative therapies. In some instances physicians, if not actually positively

recommending the process, are aiding and abetting this approach. The attraction is understandable: there is always the possibility that by some good fortune a curative regimen has been discovered. Such regimens are seldom preceded by any formal testing in patients; they avoid many of the toxic side effects of surgery, radiotherapy or chemotherapy; and there is a perception that the patient remains in control and is able to influence the course of events in a way that appears impossible with conventional therapy.

Many would agree that alternative regimens should be subjected to an enquiry no less rigorous in its attempt to assess benefit than the established procedures currently being employed to assess conventional therapies. The fact that some recent initial attempts in this country to assess the efficacy of one particular programme appeared to have serious flaws,⁴⁹ does not mean that this process is invalid and should stop. Indeed, many comparative and randomized studies of conventional treatment programmes were flawed when first introduced. It is evident that the kind of assessment necessary to deal with these new problems will go through a similar learning curve.

In the United States, where unproven cancer treatments have become a major public health issue, a study on survival and quality of life among patients attending the Livingston-Wheeler Clinic and the University of Pennsylvania Cancer Center provides a satisfactory yardstick for the planning of studies comparing alternative therapy with conventional chemotherapy. In this instance, the alternative therapy was the use of BCG and an immune-enhancing vaccine, the removal of animal products from the diet, a strict vegetarian diet of raw vegetables, and coffee enemas, compared with the cancer centre's programme of conventional chemotherapy, anti-emetic, analgesic and other support. Extremely careful matching of patients, high standards of co-operation by the alternative therapy centre, and excellent statistical analysis were a feature of the study.

The first hypothesis was that there would probably be no difference in survival between the two groups of patients, and this proved to be the case. The second hypothesis was that the quality of life of patients treated in the alternative therapy centre would be significantly better. It was very surprising that this in fact proved not to be the case. Quality of life was consistently and significantly better at the conventional cancer centre. It must be emphasized that this study, of course, only explored one type of unorthodox therapy, although the constituents of modulation of immunity, alteration of diet and the use of such unconventional procedures as enemas, are often components of these programmes. It would seem that adverse effects are even more likely with these forms of alternative therapy. The

authors conclude that any future studies in this field should include comparison with a standard orthodox palliative care group.

Conclusion

It is no less true than when the last review was written that cancer remains an intractable problem. It has also become apparent that, even within the space of 2 years, new approaches to the treatment of the most lethal of all forms of malignancy, the acute leukaemias, have been introduced and added successfully to the range of treatments available in this condition. For the first time either single agents

or combinations of established agents are beginning to show some worthwhile clinical benefit in a number of solid tumours, particularly those of the gastrointestinal tract, and the techniques of meta-analysis have shown that our first stumbling attempts in the field of adjuvant chemotherapy are in the right direction.

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