Achievements of Cancer Chemotherapy

J. S. TOBIAS, MB, MRCP (UK) and J. M. A. WHITEHOUSE, MD, MRCP

Imperial Cancer Research Fund, Department of Medical Oncology, St Bartholomew's Hospital, London

Despite advances in the recognition of aetiological factors in cancer, many patients still present with disseminated or inoperable disease. For those with malignant disease beyond the primary site, surgery alone is rarely feasible. Until relatively recently, the only useful alternative mode of therapy was radiation; the emergence of a number of different classes of antitumour drugs has provided the practical oncologist with an exciting but dangerous new tool. This short review highlights some of the genuine advances afforded by the use of aggressive drug treatment of primary and metastatic cancer and, in particular, illustrates the progress achieved in the management of the common solid tumours.

HODGKIN'S DISEASE AND THE LYMPHOMAS

Historically, Hodgkin's disease has received major attention out of proportion to its incidence. Over a hundred years ago, Bilroth (1871) deliberately employed arsenic to reduce tumour mass, and the observation of profound leucopenia following exposure to mustard gas stimulated Gilman and Philips (1946) and Wilkinson and Fletcher (1947) to use nitrogen mustard. Gratifying remissions were obtained, although it rapidly became clear that these were of short duration. Following relapse, retreatment usually failed to elicit a second response, as though a population of drug-resistant malignant cells had been left. In 1944, Heilman and Kendall demonstrated that cortisone caused regression of transplanted murine lymphosarcoma, and the synthetic steroids were employed to treat human lymphomas soon after their introduction in the early 1950s. With the emergence of further types of antitumour agents, more lengthy remissions were obtained, and the sequential use of different drugs proved to be effective in producing objective improvements in about 60 per cent of patients (Hamilton Fairley and McElwain, 1973). However, a complete remission (absolute disappearance of all symptoms, signs and evidence of disease) was achieved in only about one-quarter of all patients (Hamilton Fairley *et al.*, 1966), and no further improvement occurred until the introduction of combination drug therapy as primary treatment immediately after diagnosis. The two-drug combination of chlorambucil and vincristine was capable of producing complete remission in over 60 per cent of patients (Lacher and Durant, 1965), and this, in turn, was superseded by more aggressive four-drug regimes, notably the MOPP combination (mustine hydro-

chloride, vincristine, procarbazine, prednisolone) (DeVita *et al.*, 1970), and the MVPP combination (mustine hydrochloride, vinblastine, procarbazine, prednisolone) (Nicholson *et al.*, 1970), each of which produced complete remissions in some 80 per cent of patients treated for advanced Hodgkin's disease. It is important to stress that the successful design of combination anti-neoplastic drug regimes involves more than the random addition of a number of agents. Important principles include: the choosing of drugs that act by different mechanisms and at different sites, the avoidance of toxicity by choosing agents whose toxicities overlap as little as possible, and the selection of agents that clearly have at least some measurable single agent activity.

It is generally agreed that pulse or intermittent therapy is superior to low-dose chronic therapy since higher dosage with good host tissue recovery can thereby be achieved (Scott, 1970). The emergence of new agents of different classes has led to a proliferation of alternative drug regimes in Hodgkin's disease. Bonadonna *et al.* (1975a) employed a combination of adriamycin, bleomycin, vinblastine and imidazole carboxamide (ABVD) and reported complete remission rates comparable to those obtained with MOPP or MVPP. The potential importance of this combination lies in the probability (as yet unproven) that patients who have failed on MOPP may respond to ABVD since most of the agents in the latter combination are unrelated to MOPP components.

How important is the achievement of a complete remission? Since aggressive chemotherapy carries serious hazards, it can only be justified when patients achieving complete remission can ultimately be shown to survive longer than patients who do not respond. Hodgkin's disease has served as a useful model for answering this crucial question, and repeated series have demonstrated that responders to chemotherapy do indeed survive longer than non-responders. In a study by the South West Cancer Chemotherapy Study Group (Frei, 1972), the median survival of non-responding patients was less than 20 weeks. Those who had some (but not complete) response to therapy had a median survival of 60 weeks. After 80 weeks, 90 per cent of the patients who had achieved a complete response were still alive. Now that the majority of patients with advanced Hodgkin's disease can be put into complete remission, emphasis has shifted to the problem of when to cease therapy. Frei *et al.* (1973) treated a group of patients with six courses of MOPP and then randomised these patients to receive either no further therapy or a further nine courses of treatment at two-monthly intervals. After three years of follow-up, only 46 per cent of the first group were still in remission while 75 per cent of the latter group remained free of overt disease. It seems clear that six courses of MOPP are insufficient for most patients but further clarification is still required. As knowledge of risk factors increases, it may be possible to tailor therapy more appropriately to the individual patient; for example, it is likely that the patient with lymphocyte-depletion histology and pulmonary involvement may require more intensive chemotherapy than the

patient with lymphocyte-predominant histology and nodular/splenic disease only. Further, it is possible that patients with advanced disease would benefit from radiotherapy in addition to chemotherapy, and initial reports from the Stanford group are very promising. Patients with symptomatic Hodgkin's disease of any stage except stage IV (i.e. evidence of definite extranodal spread) were treated with combination chemotherapy (MOPP) and total nodal irradiation, and the 3-year survival rate was 100 per cent with no relapses (Kaplan and Rosenberg, 1973).

Despite these encouraging results, there remains a group of patients who do not respond to conventional chemotherapy or who relapse after completing treatment. Newer antitumour agents have been at least partially successful in these circumstances; among these adriamycin (Blum and Carter, 1974), bleomycin (Blum *et al.*, 1973a), and the nitrosoureas (Young *et al.*, 1971) appear to be the most promising. Recent cumulative data suggest that with aggressive radiotherapy, chemotherapy, and the use of newer agents, 5-year survival for all stages except stage IV is now in the order of 85 per cent; the 5-year survival of Hodgkin's disease (all patients, all stages taken together) is 81 per cent (Kaplan and Rosenberg, 1975).

The non-Hodgkin's lymphomas present more serious problems of management. First, classification of histology has proved more difficult than with Hodgkin's disease, leading to unnecessary disagreements and difficulties in comparing various methods of treatment from different centres. Indeed, at least three methods of classifying the non-Hodgkin's lymphomas are in use at present (Table 1). Second, these diseases are less predictable and may present with extranodal involvement. The majority of cases have relatively widespread dissemination at the time of diagnosis, and staging procedures are therefore of far more limited value than in Hodgkin's disease. The growing tendency is to treat patients with localised disease (especially if the histology is poorly differentiated) as aggressively as those with evidence of more advanced disease. In some centres patients with bone marrow involvement are treated as if they had acute lymphoblastic leukaemia.

In spite of these difficulties, intensive treatment of the non-Hodgkin's lymphomas with combination chemotherapy (often employing the alkylating agent cyclophosphamide, the vinca alkaloid vincristine, and prednisolone) has produced complete responses in over 50 per cent of patients; median durations of remission are significantly longer than those obtained with single-agent therapy (Luce *et al.*, 1971; Bagley *et al.*, 1972a; DeVita *et al.*, 1975).

In the earliest of these studies, complete remissions were obtained in 39 per cent of patients with histiocytic lymphoma (reticulum cell sarcoma) and in 50 per cent of patients with lymphocytic lymphoma (lympho-sarcoma) (Bagley *et al.*, 1972a). In patients achieving a complete remission, median duration of survival for both diseases was clearly improved. In histiocytic lymphoma, survival of partially responding patients was no better than that of non-responders,

Table 1. Current classifications of the non-Hodgkin's lymphomas

Lennert *et al.* (1975)	Moran *et al.* (1973)	Gall and Mallory (1942)
Malignant lymphoma lymphocytic	Well diff. lymphocytic – diffuse	Lymphocytic lymphoma
Malignant lymphoma lymphoplasmacytoid	Lymphoproliferative disease with dysproteinaemia	
Malignant lymphoma centrocytic	Poorly diff. lymphocytic – diffuse	*
Malignant lymphoma centroblastic centrocytic follicular/diffuse	Poorly diff. lymphocytic and mixed L and H – nodular (follicular) and diffuse	Follicular lymphoma
Malignant lymphoma centroblastic	Histiocytic – nodular and diffuse	*
Malignant lymphoma lymphoblastic		
B type		
Burkitt	Undifferentiated – Burkitt	Stem cell lymphoma
Non-Burkitt	Undifferentiated – Non-Burkitt	Lymphoblastic lymphoma (*)
T type		
U type		
Malignant lymphoma immunoblastic	Histiocytic diffuse	Clasmatocytic lymphoma

(* Probably classified as lymphoblastic lymphoma)

illustrating the crucial importance of eradicating all signs of overt disease. Recently, DeVita *et al.* (1975) have shown that survival with no evident disease after two years off treatment may be tantamount to cure even in patients with adverse histology (diffuse histiocytic lymphoma) since no deaths occurred after this time during a nine-year follow-up period.

CARCINOMA OF THE BREAST

A more logical approach to the management of breast cancer has slowly emerged over the past few years, partly because of a reappraisal of the role of chemotherapy. In localised disease, surgery and radiotherapy can produce survival figures of as high as 90 per cent at ten years (Carbone, 1975). Patients dying of breast cancer, however, usually die from metastatic rather than primary disease. Since each of the three major modalities of therapy act in a complementary fashion, there are grounds for optimism that multidisciplinary treatment may bring improved results.

When the primary tumour is small and the axillary lymph nodes free of disease, survival is good following surgical removal. Frequent failure is likely to occur if the tumour is large, fixed, central rather than lateral, and if the axillary nodes are involved. The results of one study showed that if one to three axillary nodes were involved, the median time to recurrence was in the order of five years. If more than four nodes were involved, median time to recurrence was only eighteen months (Cutler and Myers, 1967; Fisher, 1975). At ten years, failure rates were 24 per cent (negative axillary nodes) and 75 per cent (positive axillary nodes) (Carbone, 1975). In the U.S.A., many surgeons still favour radical mastectomy as a method of obtaining this prognostic information, although careful but more limited surgery can be equally revealing.

A surprisingly large number of agents are of known value in breast cancer, including antimetabolites such as 5-fluorouracil, antifolates such as methotrexate, alkylating agents (cyclophosphamide, melphalan), antibiotics (including adriamycin, probably the most active single agent in carcinoma of the breast) and the plant alkaloids such as vincristine (Broder and Tormey, 1974). While even the most active single agent therapy produces responses only in about 25 per cent of patients, combination therapy has at least doubled this figure. Canellos *et al.* (1974) studied 25 patients with advanced breast cancer unresponsive to hormonal therapy or endocrine ablation. Treatment consisted of cyclical courses every 28 days with methotrexate, cyclophosphamide, prednisolone and 5-fluorouracil. Seventeen patients (68 per cent) showed clear-cut responses, with seven complete responders. Median survival of non-responding patients was six months, whereas median survival of the responders could not be assessed at the time of publication. Subsequent reports of combination chemotherapy in breast cancer have confirmed that these figures can be obtained in patients treated almost entirely on an outpatient basis (Jones *et al.*, 1975; De Lena *et al.*, 1975).

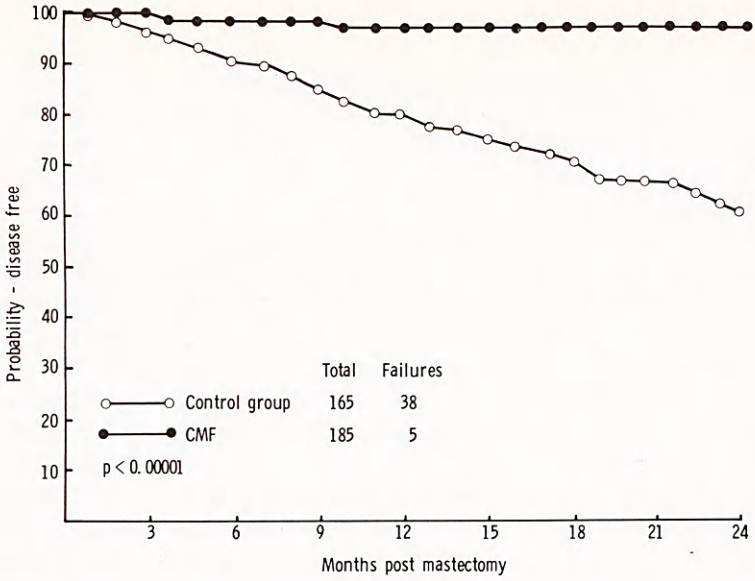

Fig. 1. Adjuvant combination chemotherapy in breast cancer. After mastectomy, patients were treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), or with no further therapy. At 2 years post-mastectomy, probability of remaining free of disease was over 95 per cent (CMF group) or 60 per cent (untreated group). (From Bonadonna *et al.*, 1976. Courtesy, *New England Journal of Medicine.*)

Since all anti-neoplastic agents are more effective against microscopic than gross disease a logical step would be to identify high-risk patients and treat them early – if possible, shortly after surgery or the completion of radiotherapy. Two recent reports have suggested that this approach may be justified. In the first, patients with primary breast cancer and involvement of axillary nodes were randomised prospectively either to a modest dose of melphalan by mouth (0.15 mg/kg for five consecutive days every six weeks) or to placebo therapy (Fisher *et al.*, 1975). Failure of treatment occurred in 22 per cent of 108 patients receiving placebo and in 9.7 per cent of 103 women given melphalan, a statistically significant difference that was even more marked in premenopausal women (in these patients failure occurred in 30 per cent of the placebo treated group and only in 3 per cent of the melphalan treated group). Further, the time to recurrence of disease was significantly greater in the patients on chemotherapy. Adverse effects from the comparatively mild treatment regime were not severe, and life-threatening myelosuppression was not seen. The second study (Bonadonna *et al.*, 1975b) adopted a more agressive approach using combination therapy. Following surgery, high-risk patients received either no treatment or treatment with cyclophosphamide, methotrexate and 5-fluorouracil for twelve

monthly cycles. Relapses occurred in 12 per cent of the untreated group and in 2 per cent of the treated group during the follow-up period, and patients with more than four axillary nodes involved were particularly likely to relapse. The long term results of this study are not yet available but a trend in favour of chemotherapy is clearly emerging (Fig. 1).

There are obvious parallels between breast cancer and Hodgkin's disease. Both are sensitive to radiotherapy and chemotherapy even when a large bulk of tumour is present. The natural history of each suggests that prognosis is improved when the disease is discovered and treated early, when the tumour burden is relatively small. Although several chemotherapeutic agents are known to be of value, a high probability of response has only occurred since the introduction of combination therapy. Additionally, some varieties of breast cancer (i.e. those with oestrogen-receptor sites) are sensitive to hormone therapy too. The logical approach to management in breast cancer includes surgery and radiotherapy to sterilise the primary areas and prevent local spread, with early chemotherapy to eradicate micrometastases before they become clinically evident. The role of hormonal therapy or endocrine ablation is unclear, although great progress has been made in the identification of breast neoplasms that are sensitive to hormonal manipulation (McGuire *et al.*, 1975).

GYNAECOLOGICAL CANCERS

The depressing lack of improvement in survival figures for ovarian cancer is the most difficult problem in gynaecological oncology today. Unlike carcinoma of the cervix, there is no reliable test to help in the diagnosis of early disease. Most patients present relatively late, and the prognosis is frequently considered to be hopeless. Although the value of removing as much tumour as possible is in dispute, most authors believe this to be worthwhile (Munnell, 1968; Aure *et al.*, 1971; Griffiths *et al.*, 1972; Hreshchyshyn, 1973). Radiotherapy is often given routinely despite minimal evidence supporting its use in this disease (Bagley *et al.*, 1972b).

Chemotherapy for ovarian cancer dates from the 1950s, when Green (1959) and Bateman and Winship (1956) demonstrated dramatic improvements – often in ascitic fluid volume but also in reduction of the size of solid masses – following courses of alkylating agent therapy. It became clear that response to single agent therapy with alkylating drugs was approximately 50 per cent, regardless of the agent used (Beck and Boyes, 1968; Smith *et al.*, 1972). Hreshchyshyn (1973) was able to demonstrate that complete responders to such therapy had a longer survival than non-responders, and Nye (1972) confirmed that a group of patients treated for advanced disease with chemotherapy survived longer than a group of matched control patients, who had the same grade and stage of tumour and had undergone similar surgery. More recently, attempts have been made to use a number of drugs simultaneously. Parker *et al.* (1975) using the synergistic

combination of adriamycin and cyclophosphamide, showed that an objective 80 per cent response rate could be obtained in previously untreated patients; this has been confirmed elsewhere (S. E. Salmon and R. E. Lloyd, personal communication). In addition to antimetabolites and antifolate drugs, three newer agents have been encouraging. Adriamycin demonstrated activity at least as good as that of melphalan in a prospective study in which responses were seen in 62 per cent of patients with very advanced (stage IV) disease (De Palo *et al.*, 1974). Hexamethylmelamine, a relatively non-myelosuppressive drug whose limiting toxicity appears to be on the extrapyramidal system, has demonstrated marked activity in ovarian cancer unresponsive to conventional alkylating agents (Blum *et al.*, 1973b). Finally, the platinum complexes, in particular *cis*-platinum (II) diamminedichloride, have produced objective remissions in very advanced disease. In one study, 7 of 19 previously treated patients who were resistant to other cytotoxic drugs achieved objective responses to the platinum complex (Wiltshaw and Carr, 1975). Since it is now clear that several different classes of agent have significant activity in ovarian cancer, use of combinations of these drugs should improve antitumour activity without increasing toxicity to an unacceptable degree. Painstaking surgical removal of bulk disease, coupled with combination chemotherapy and radiotherapy if the disease is sufficiently localised, should produce superior results to those presently obtained.

Major progress has been made in the management of gestational trophoblastic tumours (including choriocarcinoma), for two reasons. This cancer is unusually chemosensitive and its product, the chorionic gonadotrophin (HCG), has proved to be a reliable measure of disease activity. Thus, timing and intensity of treatment can be varied intelligently to cope with active disease even when the disease is not clinically apparent. There appear to be good and bad risk populations in choriocarcinoma, depending on initial HCG titre, time of initiation of therapy, and sites of metastatic disease. Cure rate in the good-risk group appears to be in the order of 95 per cent (Hammond *et al.*, 1973). The majority of these patients will require only single-agent therapy with methotrexate; in the poor-risk group, combination chemotherapy has been more successful than single-agent treatment, resulting in a cure rate of approximately 75 per cent (Hammond *et al.*, 1973; Jones and Lewis, 1974).

Following expulsion of a hydatidiform mole, aggressive therapy may be justified when the HCG is very high and uterine curettage has not proved diagnostic (*British Medical Journal*, 1974). An alternative approach has been to give prophylactic chemotherapy at the time of evacuation of a mole in order to cure microscopic disease before it becomes clinically evident (Koga and Maeda, 1968; Ratnam *et al.*, 1971). In a recent study by Goldstein (1974), patients with hydatidiform mole were treated with prophylactic actinomycin D chemotherapy and this group was then compared with a similar group of patients who had received no chemotherapy. In the untreated group, 16 patients developed

evidence of trophoblastic neoplasia whereas, in the treated group, there were only 4 such patients. Serious haemorrhage occurred in 22 of the untreated patients but in only 8 of the patients receiving chemotherapy.

Other gynaecological tumours respond less reliably to chemotherapy though some success has been achieved with adenocarcinomas of the endometrium. These have been successfully treated with methotrexate, alkylating agents or, more recently, the combination of adriamycin and cyclophosphamide (Donovan, 1974; Muggia *et al.*, 1974). Abdominal African Burkitt's tumour, which often involves the ovary, is sensitive to alkylating agent therapy but good results are obtained only if all gross disease can be removed by surgical operation. Magrath and his colleagues (1974) found that 90 per cent of patients undergoing extensive surgery and chemotherapy were alive six years later; for patients receiving chemotherapy but no operative removal, the figure was less than 40 per cent and for patients undergoing partial resection, survival was just under 50 per cent at five years. The importance of this study was to underline the need for bulk tumour removal to reduce tumour burden as well as to emphasise the need for a multimodal approach in which co-operation between surgeon and chemotherapist was of the utmost importance.

TESTICULAR TUMOURS

Testicular malignancies constitute 13 per cent of all cancers in men between the ages of 20 and 40 years. Though pure seminomas are very sensitive to radiotherapy and chemotherapy (with a five-year survival rate of over 90 per cent), the non-seminomatous germ cell tumours (teratomas, embryonal cell carcinomas, choriocarcinomas and mixed tumours) carry a far worse prognosis. Many anti-neoplastic agents have been employed for this group of diseases, with an overall complete response rate of about 10 per cent and a rather short duration of remission measured in months (Livingstone and Carter, 1970). Recently, interest has centred on the use of two drugs with more marked activity, vinblastine and the Japanese antibiotic bleomycin. Samuels (1970) treated 21 patients with vinblastine, and observed 11 responses (4 complete). A summary of experience with bleomycin showed that 11 responses (one complete) were obtained in 37 patients given the drug (Agre, 1970). Since the spectra of toxicities for these agents do not overlap, full doses have been employed in a number of studies. In the first of such series, the results were sufficiently encouraging to justify previous claims of therapeutic synergism; 17 out of 19 patients showed objective responses, with 3 complete responders (Agre, 1970). In a larger group of 50 patients, all with stage III germinal cell neoplasia of the testis, Samuels *et al.* (1973) observed 16 complete responders and 22 partial responders. Fifteen of the 16 complete responders were alive and disease-free for up to two years after diagnosis. Eleven further patients were treated with the combination, resulting in 5 complete and 4 partial responders with only 2 patients failing to show any

response at all (Spiegel and Coltman, 1974). Recently, Samuels *et al.* (1973) have used continuous infusions of bleomycin with intermittent vinblastine, on the grounds that increased duration of exposure to the drug is known to reduce the fraction of surviving cells (Drewinko *et al.*, 1972). Of 23 patients with very advanced (stage III) germ cell neoplasm, 17 responders (9 complete) were seen, suggesting that this regimen may be superior to pulse therapy with bleomycin and vinblastine (Samuels *et al.*, 1975). Eight of the complete responses occurred in patients with massive disease in whom a low rate of response was expected. Surprisingly, previous treatment with chemotherapy did not affect response rate, most patients in this series having already failed to respond to actinomycin D. There are good theoretical data to support the use of this combination since bleomycin appears to be most active against cells in mitosis, whereas vinblastine is a potent spindle poison that arrests cell division in mitosis (Barranco and Humphrey, 1971). Since testicular neoplasms predictably metastasise to the lungs, the preferential accumulation of bleomycin in the lung may partly explain its efficiency in these diseases (Umezawa *et al.*, 1967). Of the other agents available, it is worth mentioning that mithramycin, an anti-neoplastic antibiotic obtained from *Streptomyces plicatus,* has produced durable and complete remissions in many patients. Kennedy (1972) described 52 patients in whom responses to mithramycin were well documented in 25; 15 of these (29 per cent) were complete responses. Although mithramycin causes a haemorrhagic diathesis in a significant number of patients, the use of alternate day therapy has reduced the incidence of this complication from 59 per cent to zero, although marked disturbances of liver and renal function, gastrointestinal complaints, malaise and abnormalities of calcium metabolism still occur. Optimal management of testicular tumours will almost certainly include early post-operative treatment with combination chemotherapy though the ideal regime must await the development of even more effective drugs with less serious toxicities than those used at present.

MYELOMATOSIS

The diagnosis of myeloma frequently rests on the demonstration of a homogeneous paraprotein band in the plasma as well as other typical features, and the width of this band is often used to assess progress. Multiple myeloma is a relatively slow-growing malignancy with a variable spectrum of manifestations so that clinical response to chemotherapy may be difficult to measure. Using the width of the paraprotein band and an estimate of paraprotein production per myeloma cell, Durie and Salmon (1975) have devised a method of computing the absolute number of myeloma cells present and have shown that the absolute number of cells influences the aggressiveness of the disease process as measured by performance status, weight loss, serum albumin, degree of anaemia and so on. Cellular response to chemotherapy could also be measured by this method, and it

was demonstrated that effective chemotherapy reduced the tumour burden by 90-99 per cent (1-2 logs). Although this is a much smaller figure than is usually required for successful chemotherapy, the rate of progression in myeloma is sufficiently slow for this reduction to result in real improvement in patients who respond to treatment. In such patients, the median duration of survival of nine months in untreated patients has been more than doubled (Malpas, 1974).

Despite this figure, the chemotherapy of myeloma remains unsatisfactory. Many physicians use the schedule of Alexanian *et al.* (1972), consisting of intermittent treatment with melphalan and prednisolone every six weeks, although cyclophosphamide was shown to be as effective as melphalan in an M.R.C. randomised controlled trial (M.R.C., 1971). The question of response to alkylating agent therapy following failure to respond to a different alkylating agent has been studied by Bergsagel *et al.* (1972) who treated melphalan-resistant patients with large intermittent doses of cyclophosphamide. Objective responses were seen in 11 out of 19 patients. In experimental tumours, Schabel *et al.* (1975) have demonstrated that melphalan and cyclophosphamide may indeed be synergistic, which implies that the drugs may operate through different mechanisms. Other recent attempts to improve chemotherapy for myeloma have included an assessment of the role of vincristine and procarbazine (South West Oncology Study Group, 1975) though neither of these agents added to the response rate seen with conventional melphalan-prednisolone therapy. A small trial by Azam and Delamore (1974) has suggested that initial therapy with BCNU, cyclophosphamide, melphalan and prednisolone may be more effective. During the 18 months study period, only one of 19 patients died, probably of hyperparathyroidism rather than myeloma *per se.* Use of this intensive regime appeared to be of particular value in patients who had a high blood urea and were very ill when first seen, i.e. patients with a poor prognosis (M.R.C., 1971). Every patient demonstrated an improvement in paraprotein level, in contrast to all previous studies employing single-agent chemotherapy with or without prednisolone. Studies *in vitro* suggested that the combination exhibited synergistic cytotoxic effects, and cell kill was greater than with any of the constituent agents used alone. If the results of this study can be confirmed these data will represent good evidence that alkylating agents can usefully be employed in combination, apart from providing significant progress in the management of multiple myeloma.

PAEDIATRIC TUMOURS

Since the management of paediatric tumours has been well reviewed (Evans, 1974) and represents a major specialty in its own right, only a few topics will be dealt with here. The treatment of cancer in the paediatric age group has been revolutionised since the introduction of chemotherapy by Farber *et al.* (1948) who reported brief remissions in children with acute lymphoblastic leukaemia treated with methotrexate. This disease has proved to be sensitive to a large

number of anti-neoplastic drugs, and its prognosis has been dramatically improved by the use of combination drug treatment both for induction and maintenance of remission, as well as by the routine use of prophylactic radiation and chemotherapy to the central nervous system (Pinkel, 1971). At the present time, some 55 per cent of children with acute lymphoblastic leukaemia are surviving, apparently cured, at five years, and the question of when to stop treatment has become a very real one (Aur *et al.*, 1974). Farber also pioneered the use of actinomycin D for Wilms' tumour (nephroblastoma), and the management of this disease has rapidly advanced since the widespread use of adjuvant chemotherapy following surgery. Simple surgical removal of localised primary disease produced durable remissions in up to one-third of patients (Ladd, 1938), with further benefit (up to 50 per cent survival at five years) from postoperative radiotherapy (Gross and Neuhauser, 1950). Use of sequential courses of actinomycin D therapy has led to survival rates as high as 80 per cent for those patients presenting with localised disease (Wolff *et al.*, 1974). A prospective study of patients with Wilms' tumour showed that the use of actinomycin D for five months following surgery reduced the incidence of metastatic disease from 50 per cent to 20 per cent (Wolff *et al.*, 1968).

One of the most dramatic observations in paediatric oncology over the past few years has been the recognition that osteogenic sarcoma is a chemosensitive disease that may even be curable. Until recently, the disease had a uniformly grave prognosis since 50 per cent of affected children developed pulmonary metastases as little as six months after removal of the primary tumour. In 1972, Jaffe reported that very large doses of methotrexate followed by 'rescue' of the normal host tissue by folinic acid (citrovorum factor) could be effective in reducing the size of pulmonary metastases though cures were not possible since such gross disease was already present. This prompted Jaffe and his colleagues (1974) to institute routine postoperative therapy with high-dose methotrexate and citrovorum factor, so that micrometastases in the lungs could be eradicated before they had become clinically apparent. Twenty consecutive patients received adjuvant therapy within three weeks of local treatment of the tumour. During the study period, the incidence of pulmonary metastases was reduced from the expected 12 cases to two cases. Nineteen of the twenty patients treated with adjuvant chemotherapy survived, with follow-up periods of up to 23 months (Fig. 2). It also became clear from a study at Rosewell Park Memorial Institute that this tumour was sensitive not only to methotrexate but also to adriamycin (Cortes *et al.*, 1974); at present preliminary studies with adriamycin-methotrexate chemotherapy of osteogenic sarcoma are in progress and have been encouraging, (N. Jaffe, personal communication).

Progress has also been made in the management of rhabdomyosarcoma of childhood. As with Wilms' tumour, the best results have been obtained where a multimodal approach has been adopted. The agents that have been most useful are

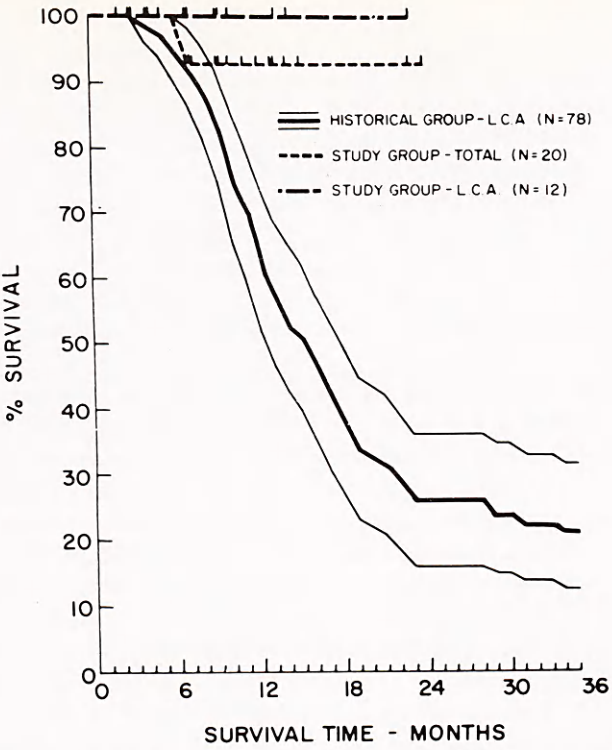

Fig. 2 Survival in patients with osteogenic sarcoma treated by amputation alone (historical group) or with adjuvant chemotherapy using high doses of methotrexate with folinic acid rescue. Prior to the use of chemotherapy, median survival time was less than 18 months. L.C.A. = local control achieved, usually by radical surgery. Narrow continuous lines show 95 per cent confidence limits for the historical group; vertical check marks indicate the time of last follow-up examination. (Courtesy *New England Journal of Medicine.*)

actinomycin D (regression of tumour was seen in 26 per cent of 38 patients), vincristine (regression seen in 50 per cent of 20 patients) and cyclophosphamide (regression seen in 57 per cent of 37 patients) (Pratt, 1969). When these three drugs were combined, 76 per cent of 21 children treated for inoperable or metastatic disease were alive without evidence of recurrence, with follow-up periods of up to four years (Wilbur *et al.*, 1971). The overall survival of children with rhabdomyosarcoma treated with surgery and/or radiotherapy is approximately 12 per cent (Jaffe *et al.*, 1973); with the addition of combination chemotherapy, overall survival now averages about 30 per cent in most large centres (Raney *et al.*, 1974). Of the newer agents employed in this disease, the most promising is adriamycin; in a small series of previously-treated children, this drug produced responses in as many as 80 per cent of patients (Raney *et al.*, 1974).

CONCLUSIONS

In a remarkably short period of time, chemotherapy with anti-neoplastic drugs has become an established part of the treatment of a variety of malignant diseases. Certain drug-sensitive tumours have served as models for the derivation of principles regarding the optimal use of such agents. It has become clear that the use of cytotoxic drugs need not be accompanied by unacceptable toxicity, and a greater understanding of the unwanted effects of these drugs has led to the design of safer schedules. At the present time, the casual use of antitumour drugs must be considered dangerous and should be discouraged. Optimal methods of treatment will be defined only if patients are treated in large centres where facilities and experience are sufficient to cope with the hazards of cancer chemotherapy.

Combination chemotherapy has become established as standard treatment for Hodgkin's disease and the adult and childhood leukaemias, the non-Hodgkin's lymphomas and several non-haematological childhood tumours. It seems likely that combination drug therapy will also become more widely employed in the treatment of cancer of the breast, ovary and testis since a number of carefully controlled studies in these diseases have had encouraging results. The greatest benefit from cancer chemotherapy is obtained when an aggressive approach is adopted early in the disease, and the results obtained with early therapy following surgery for breast cancer and osteogenic sarcoma of childhood are particularly exciting since principles derived from basic tumour biology and animal experimentation would predict a high rate of response when anti-neoplastic drugs are given as adjuvant treatment. The cancer chemotherapist is, by definition, an aggressive physician; to improve results he must treat intensively at a time when the surgical and radiotherapeutic attack has reduced tumour burden to a minimum. As more and more tumours prove to be at least partially sensitive to drug therapy there is reason to be optimistic that survival figures in common cancers will significantly improve over the next ten years.

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