swelling in 7-10% of cases; whereas axillary clearance followed by radiotherapy causes swelling in 33% of cases.

Many patients develop temporary minor swelling of the arm immediately after mastectomy.[5] If severe, swelling at this time is likely to be caused by axillary vein thrombosis because lymphoedema takes many weeks to develop.[6] Minor swelling that is still present one month after operation and is getting worse is likely to be lymphoedema, but another cause is compression of the axillary vein by scar tissue. Oedema of the arm may also begin many years after mastectomy.[5,6] The commonest cause is recurrent disease in the axilla causing venous or lymphatic obstruction but occasionally it is progressive obliteration of the lymphatics secondary to the surgical or radiation lymph node damage (the die back phenomenon).[7]

Lymphoedema of the arm, whether primary or secondary, is best managed by simple conservative measures. Firstly, encouraging the patient to wear a good quality arm stocking and tight elasticised glove; secondly, massaging the arm centripetally twice a day; and, thirdly, raising the arm in a sling or on pillows above heart level at night and using a pneumatic compression legging by day, and if possible throughout the night as well.

When the arm is so swollen and heavy that the shoulder joint beomes painful, clothes never fit, and flexion of the elbow is restricted the surgeon may employ the same types of reducing operation used on the leg.[8] The only cosmetically acceptable procedure is the simple excisional (Homans's) operation. The medial side of the arm and forearm is treated first, succeeded three months later by the same procedure on the lateral side. The size of the fingers cannot be diminished and the results of the procedure on the back of the hand are often unsatisfactory. The frequent minor complications of reducing operations such as necrosis of the edges of the skin flaps and loss of cutaneous sensation cause more trouble and distress in the arm than they do in the leg. Nevertheless, the operation often substantially improves both the symptoms and the appearance so that it is worth while in patients with gross oedema and no recurrence of their primary disease. No longer is it acceptable to tell a patient with postmastectomy oedema that she must accept the discomfort and gross disfigurement as the price of survival when the surgeon can help considerably, with both conservative treatment and surgery.

N L BROWSE

Professor of Surgery,
St Thomas's Hospital,
London SE1 7EH

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Regular Review

Advances in managing childhood cancer

P MORRIS JONES

The 1960s and early 1970s saw important advances in treating childhood malignancy, and by the late 1970s more than half of childhood cancers were curable. These cure rates were not achieved, however, without the risk of treatment causing problems in the future. The improvements did not come through any single breakthrough but rather by the cooperation of paediatric oncologists, haematologists, radiotherapists, surgeons, pathologists, and research workers supported by many paramedical professions.

As the newer more intensive multidrug treatments were used some children succumbed to infections, drug toxicity, and metabolic complications, but as supportive care improved death in remission became less common. The intensity of treatment has actually been reduced in certain groups once a good prognosis has been established—for instance, only 50-60% of all children with nephroblastoma now need radiation treatment and most children with Hodgkin's disease are cured by chemotherapy alone (even those with regional or disseminated disease).

The difficulties presented by the small numbers

These important advances could not have been achieved without the referral of patients to regional centres, where they can be entered into national and international studies of treatment regimens. The rarity of childhood cancer (1 in 10 000 children affected each year) makes multicentre studies essential as no one doctor can gain enough experience or accrue enough patients to assess accurately the impact of a new treatment. The Americans led the way with their cooperative study groups, which were imaginatively supported by major grants from government sources; they allowed the groups all over the United States to concentrate their resources on solving the problems without concern for the costs to the patients.

These groups have recruited most cases of childhood cancer into nationally conducted controlled trials since the 1960s, and the success of this policy has been clearly shown in the paper of Miller and McKay on reductions in childhood

cancer death rates from the 1950s.[1] In Britain the development of cooperative studies lagged behind the United States except for the Medical Research Council trials in childhood acute lymphoblastic leukaemia; these have recruited most patients and now show survival rates equal to those of the United States.

The few children in Britain with cancer (1400 new cases each year) makes randomised studies difficult to organise as significant differences in survival cannot be shown. Patients can, however, be stratified according to the extent of spread of disease and by histological or cytological subgroup and by other established prognostic factors. The United Kingdom children's cancer study group has several such studies underway and is generously funded by national and local charitable sources. These bodies seem more aware of the need for such studies than the government sources.

Using the old drugs more efficiently

Many hurdles are still to be overcome, and problems will probably not be solved by manipulating current treatments. Little is to be gained from screening procedures, except perhaps for neuroblastoma by estimating the excretion of catecholamines and their metabolites. This technique has been used in Japan in a similar way to screening newborn infants for metabolic disorders, and Sawada *et al* claim an appreciable detection of early tumours.[2] Neuroblastoma diagnosed in the first year of life has a much improved prognosis, and if screening can pick up these tumours in a preclinical phase it will be a great advance.

Serum α fetoprotein concentrations are raised in patients with hepatoblastomas and some germ cell tumours, but these tumours are so rare that screening is impractical. Because most childhood tumours are deep seated, physical examination is not likely to detect early tumours.

As more specific tumour markers are found, especially those of chromosomal deletions and translocations and oncogenes, family members will probably be screened to identify those at risk. Reappraising our present treatments is more likely to bear fruit than hoping for new drugs. Continuing research for new drugs is essential, but the yield is small. Many of the older combinations of drugs were originally devised empirically and were not necessarily based on pharmacological data. Yet pharmacological advances that have been made combined with information from in vitro studies of the effects of the drugs on various human cancer cell lines may well lead to better use of the drugs. Likewise, more is known about the interactions between drugs leading to variable bioavailability of the cytotoxic agents.[3] Further studies of this kind may increase the efficacy of established agents.

Using autologous bone marrow transplantation to rescue patients from otherwise lethal doses of cytotoxic agents is another treatment that is increasing in popularity. The rationale for this intensive treatment is that a tumour is most sensitive at the beginning of treatment and that it is more likely to be destroyed at this time before resistant cell lines emerge. Drugs that have already been tested clinically include methotrexate, cytarabine, and melphalan. An alternative strategy is to use many different agents in quick succession to achieve remission consolidation and further intensification. This method is well illustrated in the highly successful protocol introduced by Wollner and others for treating non-Hodgkin's lymphoma.[4]

Toxicity problems

These treatments are all very toxic, are accompanied by appreciable morbidity and mortality, and require very careful monitoring of the patients. Immunosuppression leads to an increased risk of infection and is caused by neutropenia and disturbed neutrophil function and changes in humoral and cell mediated immunity. The commonest bacterial pathogens tend to vary from one unit to another, but coagulase positive and negative staphylococci and *Pseudomonas pyogenes* are important. All pyrexial patients with neutropenia need empirical treatment with a combination of antibiotics until an organism is isolated or the fever settles. Varicella and herpes zoster and simplex can now be successfully treated with acyclovir, but measles remains a major killer in British children because of the low uptake of measles immunisation. Opportunistic infections—for instance, with *Pneumocystis carinii*—are a continuous threat, and supportive care and barrier nursing techniques are thus very important.

The greatest improvements

One of the greatest improvements in survival in recent years has been achieved in acute lymphoblastic leukaemia. Careful evaluation and the application of statistical criteria has allowed the delineation of prognostic factors, which in turn has enabled patients to be stratified into groups which can be treated differently. Survival from childhood leukaemia in patients diagnosed within the past few years is about 70% or greater.[5-7]

Great strides have also been made in treating osteogenic sarcoma. Until the introduction of very high dose treatment with methotrexate and the use of adriamycin and cisplatin less than a quarter of patients with this tumour survived, and most had to cope with amputation and multiple lung metastases. Now preoperative chemotherapy, endoprosthetic replacement of the diseased bone, and further chemotherapy has changed prognosis and led to a fall in metastases; this has enabled surgeons to be aggressive in their resections, and survival rates are now 70%. The early results from endoprosthetic replacement are satisfactory with excellent function, especially for femoral replacement. In Britain most of this surgery has been carried out in two orthopaedic centres, which has enabled considerable expertise to accrue.

Children who present with or develop metastatic disease from nephroblastomas, rhabdomyosarcomas, and germ cell tumours may be cured by using either more intensive protocols or second line treatment. Even children who relapse after treatment for acute lymphoblastic leukaemia are being cured by either further drug treatment or bone marrow transplants. The chance of cure in these patients is closely related to the length of time off treatment before relapse.

In some paediatric cancers the results remain unsatisfactory—in particular the malignant brain tumours, neuroblastomas with bony metastases, and Ewing's tumour. Cooperative trials of chemotherapy (usually using vincristine and a nitrosourea) have shown benefit in certain categories of patients with tumours of the central nervous system, in particular in children aged under 2 with medulloblastomas, those in whom only biopsy or partial excision of the tumour is possible, and those in whom the brain stem is affected. Unfortunately, not all children with such tumours currently receive optimum treatment because they are not referred to paediatric oncology or radiotherapy centres.

Bone marrow transplantation

Both allogeneic and autologous bone marrow transplantation have a place in managing childhood cancer, but they should not be considered to be cure alls. They are alternative treatments that are sometimes first line therapy —for example, autologous transplantation in acute non-lymphocytic leukaemia where there is a suitable donor offers a greater chance of cure than chemotherapy alone. Likewise, some children with acute lymphoblastic leukaemia can benefit from transplantation in first remission if they are in the high risk group that is less likely to do well with chemotherapy. After relapse more children can be retrieved with a transplant than by chemotherapy, but long term survival is achieved in only about 20% of this group.

Autologous transplantation—with or without purging of the marrow—is gaining in popularity. Purging is achieved by using monoclonal antibodies to neoplastic differentiation antigens. The antibodies are used either with complement or coupled to ricin or magnetic beads. Afterwards the marrow is reinfused either immediately after high dose, short acting drugs such as melphalan or after cryopreservation and subsequent intensive treatment. A similar technique of attaching monoclonal antibodies to liposomes and then both to a toxin, chemotherapeutic agent, or radionuclide allows specific targeting of the destructive agent to the cancer cells.

What price must be paid?

Most of these modern treatments are associated not only with early toxicity but also with late unwanted effects.[8] A price has to be paid for the lives of these children. Many of the radiation effects have been well described and include hormone deficiencies because of the failure of various endocrine organs included in radiation fields. Thus, children receiving cranial radiation of 3000 cGy or greater to an area that includes the pituitary fossa will show growth hormone deficiency. Thyroid failure will occur with therapeutic doses of radiation to the neck, and gonadal failure occurs after abdominal or testicular irradiation.[9] Total body irradiation causes all three types of endocrine failure. Newer radiation techniques will minimise some of these problems, but they cannot be completely prevented.

As yet the extent of the later effects of chemotherapy programmes are unknown. Certainly some produce sterility,[10] and others (especially the alkylating agents such as nitrogen mustard, cyclophosphamide, and chlorambucil) are oncogenic. Increasing numbers of second malignancies are being reported in children treated with drugs alone[11] as well as in those treated with radiation.[12] We have probably not yet seen the peak for these second tumours.

The long term uncertainty puts an immense strain on the families of children with cancer. When cure rates were low the families had to cope with the grief of the loss of a child—but the illness itself was short. Now, with much longer periods of treatment, the threat of death remains, and there may be psychosocial problems for the child and family who find adjustment difficult. The use of specially assigned social workers (mostly supported by the Malcolm Sargent Children's Cancer Fund) and of liaison nurses has led to a better understanding of these problems, and pre-emptive counselling has gone some way towards alleviating the stress.

The future

What are our future goals? Firstly, we must concentrate on the presently incurable cases, which requires cooperation between groups. The numbers of children available will be less and hence the questions will take longer to answer—so greater efforts are necessary to recruit patients into studies planned specifically to improve outlook in the later stage cases and in the high risk groups. Long term follow up of these patients is imperative both for monitoring late effects of treatment and for conducting further epidemiological and genetic studies. Unless a method is devised for keeping these patients under regular review many aetiological clues will be ignored.[13] Our success means that we owe a debt to the patients to continue to improve their quality of life and to strive for prevention rather than cure.

P MORRIS JONES

Reader in Child Health (Paediatric Oncology),
Royal Manchester Children's Hospital,
Pendlebury M27 1HA

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