Today's Treatment

Blood and Neoplastic Diseases

Solid Tumours in Children

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British Medical Journal, 1974, 4, 710-713

Introduction

From the age of 1 to 15 malignant disease is the commonest disease causing death in Britain and the commonest cause of death after accidents, poisoning, and violence. The incidence of malignant tumours in the Manchester region is shown in table I. In the past decade, however, there have been major advances in the treatment and prognosis of some types of childhood malignancy. For example, in acute lymphoblastic leukaemia dramatic improvements have resulted from the use of more effective combination chemotherapy regimens, augmented by radiotherapy in the prophylactic treatment of the central nervous system, so that leukaemia-free five year survival rates of over 50% have now been reported.¹

TABLE I—Manchester Children's Tumour Registry: Incidence of Malignant Disease 1954-68

Disease	Incidence %
Leukaemia	29.4
C.N.S. tumours	28.3
Connective tissue tumours rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma etc.	13.6
Non-leukaemic reticulo-endothelial tumours. Non-Hodgkin's lymphomas, Hodgkin's disease etc.	9.7
Renal tumours	5.5
Teratomas	3.1
Epithelial tumours	3.1
Miscellaneous	5.5

C.N.S. = Central Nervous System.

Similar improvements are now expected in the treatment of the solid tumours of childhood after the application of vigorous multidisciplinary treatment policies by special units combining expert paediatric surgery, radiotherapy, and multiple drug chemotherapy regimens. The control of the complications of treatment such as infection, to which these children are particularly prone, has also made a major contribution to the improvements in survival.

Diagnosis

The proper treatment of a child with malignant disease must be based on accurate diagnosis and this is secured only by a

adequate biopsy—which should be an open biopsy wherever possible. When an accessible lymph node is involved, the entire node with its capsule intact should be removed from a site where the disease is known to have been present longest. Modern techniques have improved the accuracy of histological diagnosis; for example, electron microscopy to detect the striated muscle cell or rhabdomyoblast or the features of renal epithelium in Wilms's tumour, and special staining techniques such as the periodic acid Schiff (PAS) stain to detect cytoplasmic glycogen in rhabdomyosarcoma and in Ewing's sarcoma. In neuroblastoma a definite histological diagnosis is often unobtainable from semi-solid haemorrhagic or necrotic biopsy material, but the detection and the measurement of urinary catecholamines such as vanillyl mandelic acid (VMA) may lead to the diagnosis and enable the progress of treatment to be monitored.

Once malignant disease is confirmed the extent of spread must be assessed. Premature treatment may make it difficult if not impossible to define accurately the extent of the disease and thus prejudice proper management. An agreed system of staging is frequently employed which describes the extent of the disease and enables results from different centres to be reported and compared. Any staging system only reflects current knowledge of those aspects of disease spread that relate to prognosis and so may require modification with time.

The process of staging requires an interdisciplinary approach which will involve the surgeon, physician, paediatrician, radiologist, haematologist, and pathologist. There is no substitute for a good history and physical examination, and aids such as photography to record the findings should be freely employed. The bone marrow should be examined frequently as this site is more frequently involved than is appreciated, particularly in neuroblastoma and rhabdomyosarcoma. Radiography of the chest, often including whole-lung tomography, and a skeletal survey should be done and may reveal unsuspected metastatic disease. Intravenous pyelography in children with abdominal and pelvic tumours not only assesses renal size, shape, and function, but is useful to demonstrate renal or ureteric displacement by tumour masses or involved lymph nodes. Lymphangiography is now a well-established investigative procedure in the malignant lymphomas such as Hodgkin's disease and in some other tumour types. It can show the presence and extent of lymph node involvement in inguinal, iliac, and para-aortic node areas and because the dye is often retained in the nodes for many months it can serve as a useful guide to therapeutic response or subsequent reactivation of the disease.

The role of bone-scanning and tumour localization with radionuclides such as technetium-99m and indium-III-bleomycin is currently under investigation. For children the use of a gammacamera for scintiscanning has a great advantage over the rectilinear scanner as it enables a rapid picture of isotope uptake to be taken. An assessment of liver and kidney function is particularly important in children with malignant disease, not only as a measure of involvement by the disease process itself, but also as a measure of the patient's ability to metabolize

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cytotoxic drugs and excrete the breakdown products from tumour cell destruction. In radio- and chemo-sensitive tumours such cellular breakdown products may present a heavy burden to an excretory system perhaps already impaired by disease. Accurate and up-to-date knowledge of the peripheral blood count is an essential part of the general assessment and as a preliminary to the start of any form of treatment. Such general factors as the child's nutritional state, infection, or mental disturbances are of obvious importance and will have a direct bearing on management.

Treatment of Specific Tumours

NEUROBLASTOMA

Neuroblastoma is the commonest solid tumour in children, over half the cases occurring before the age of 2. It may arise from the adrenal or from sympathetic tissue at any site. There is a considerable variation in the biological behaviour and, though maturation and even spontaneous regression have been recorded, most spread locally and soon metastasize.

The two most important determinants for survival are the stage of the disease at presentation and the age of the child. In general, children with local disease survive longer than those with regional disease. If the disease is disseminated, particularly if the bones are involved, the prognosis is bad. Children under 1 year have a better prognosis than older children, and a few infants show spontaneous recovery. Treatment of local or regional disease should be surgical, with removal of the whole tumour or as much of it as possible. After partial removal of the tumour radiotherapy to the residuum definitely improves the prognosis. A "second look" by the surgeon if the tumour responds but is still present after radiotherapy is worth consideration. Children with disseminated disease will respond to chemotherapy.

Cyclophosphamide and vincristine are established effective agents. They may be combined and given on an intermittent schedule. Daunorubicin and adriamycin are both effective against neuroblastoma, and either combined with cyclophosphamide and vincristine may improve the response rate and extend the median duration of survival—but this regimen does not increase the number of children cured.² The use of surgery, radiotherapy, cyclophosphamide, and vincristine improves the prognosis in children under 2.³

Catecholamine determinations are helpful in confirming the diagnosis. High levels of excretion in the urine which fail to return to normal after therapy indicate a poor prognosis. A rise in the level heralds a recurrence of disease in those patients who are secretors.

WILMS'S TUMOUR

Nephroblastoma constitutes nearly 10% of all solid tumours in childhood, most occurring under 5 years. Classically presenting as a rapidly-growing abdominal tumour, it may attain massive proportions before penetrating its pseudocapsule and invading the renal bed. Lymphatic spread to the para-aortic nodes may occur, but it is the early development of bloodstream spread and pulmonary metastases that usually determine the outcome of the disease.

The diagnosis is usually established quickly from the clinical findings, intravenous pyelography, and nephrectomy accomplished within 24 hours of admission with the minimum of tumour palpation. Staging is based on the surgical findings and confirmed later by the pathologist, and determines the subsequent management.

Until 1960 the standard treatment consisted of nephrectomy followed by radiotherapy to the renal bed and lymphatic drainage to eradicate residual abdominal disease. However, for over half the children, who already had occult pulmonary metastases at the time of surgery, or who were destined to develop

them later, this was inadequate treatment. Since 1960 much evidence has accumulated to support the value of systemic chemotherapy, when added to the basic regimen in eradicating occult metastases and greatly improving survival rates.

At first actinomycin D was used at the time of operation only, followed by a prophylactic course of either actinomycin D or vincristine for one and a half to two years as in the recent Medical Research Council Wilms's trial. Now recent reports from the National Wilms's Tumour Study Group in the U.S.A. indicate that these two drugs used together give better results than one alone, and that a greater than 80% survival rate may be achieved. Adriamycin and cyclophosphamide are also effective, and their value in combination with actinomycin D and vincristine is currently under investigation in children with advanced disease.

The role of routine abdominal radiotherapy has been questioned in the management of cases with tumour confined to the kidney and completely removed; it has been safely omitted in infants under 1 year; current trials may re-define the role in older children. Routine preoperative abdominal irradiation does not offer any benefit and improved surgical techniques have now eliminated its previous indication of "doubtful operability." Children with pulmonary metastases at diagnosis or later can now be treated very effectively by combination chemotherapy, whole lung irradiation, and nephrectomy where possible, and survival rates of 50% are now attained.

With such greatly improved survival rates, present studies are attempting to re-define the role of radiotherapy and chemotherapy combinations to reduce the severity and incidence of normal tissue damage in survivors.

RHABDOMYOSARCOMA

Rhabdomyosarcoma is the commonest of all the soft tissue sarcomas and the third commonest solid tumour in children. It occurs in three principal sites: the head and neck, the genitourinary tract, and the limbs. It is a highly malignant tumour, often growing rapidly, invading locally, and becoming widely and early disseminated by lymphatic and blood stream spread.

In practice, complete surgical removal is possible only in certain favourable sites such as the orbit and the genitourinary tract, but even major exenteration procedures fail because of local recurrence or distant metastases. Radiotherapy and chemotherapy may achieve some degree of tumour regression, but with radiotherapy alone or after surgery, and followed by sequential chemotherapy, a five-year survival rate of only 40% was the best reported figure in 1966.

Nevertheless, with the recent development of intensive treatment regimens, in which triple chemotherapy is combined with surgery and radical radiotherapy, there has been a dramatic improvement in results. The administration of the three effective drugs, vincristine, actinomycin D, and cyclophosphamide, in regular intravenous pulses throughout a course of regional high-dose radiotherapy, with expert nursing care of the often severe but transient side effects, and continuation therapy for at least a year, has achieved complete regression of disease in over 80% of cases, with 75% two-year survival rates, even in the previously unfavourable head and neck group.⁴ Such is the effectiveness of this initial intensive regimen that major mutilating surgical procedures—for instance, orbital or pelvic exenteration—are no longer justified as the initial therapeutic attack but are best deferred in the locally or regional advanced case until radiotherapy and chemotherapy have achieved maximal regression. Radical surgical removal of residual disease or local recurrent disease should always be considered.

Recent experience at St. Bartholomew's Hospital⁵ in a group of nine children, seven of whom had locally advanced disease, confirms the value of these new regimens when compared with an earlier group treated by surgery and radiotherapy alone (fig. 1).

FIG. 1—Disease-free survival in seven of nine children with rhabdomyosarcoma treated with radiotherapy and concurrent combination chemotherapy compared with 17 treated with surgery and radiotherapy.⁵

HODGKIN'S DISEASE

Hodgkin's disease has been said to have a worse prognosis in children than in adults; with correct investigation and treatment this is not true. It must be emphasized that this disease is curable, particularly in its early stages. The principles of investigation and treatment of this disease and non-Hodgkin's lymphoma have already been dealt with in this series.

RETINOBLASTOMA

Through the development of modern treatment methods in special units, cure with preservation of vision is now possible in most children with this very rare malignant intraocular tumour. In a genetically-determined disease with a death rate of less than 10%, most affected children will survive as genetic carriers to pass the disease on to subsequent generations. Early and expert ophthalmic assessment is therefore mandatory for the infant at risk or for any child on the slightest suspicion.

In the established case treatment methods range from photocoagulation and cryosurgery for the smallest tumours; radioactive cobalt disc applicators for the larger single tumour; and external beam radiotherapy for the more advanced tumours. The indication for primary removal of an eye is strictly limited to the eye being found to have involvement of the optic nerve. Intensive chemotherapy and radiotherapy techniques are currently being assessed in the treatment of the child with disseminated disease, but it remains to be seen whether the length of remission and the quality of survival justify such efforts.

EWING'S SARCOMA

Ewing's sarcoma is a rare tumour of childhood. It occurs most frequently in the long bones, usually the femur, but may occur anywhere in the skeleton. It metastasizes rapidly to the lungs, other bones, and brain. Treatment with surgery and radiotherapy has given a cure rate of less than 10%. Chemotherapy affects the tumour—and vincristine, cyclophosphamide, actinomycin D, and adriamycin are all effective.

A definite improvement in the outlook has occurred recently with intensive radiotherapy to cure the local lesion and concurrent combination chemotherapy to deal with microscopic

metastatic deposits. The use of two or more agents has significantly reduced the relapse rate. The awareness that local recurrence occurs and resection may be possible has also improved the outlook. Rosen *et al.*⁶ combined dactinomycin, adriamycin, vincristine, and cyclophosphamide and have achieved long-term survival. Of 12 children treated all are alive and well with no evidence of disease from 10 to 37 months later which contrasts markedly with their previous experience (fig. 2).

FIG. 2—Disease-free survival of 12 children with Ewing's sarcoma treated with radiotherapy and adjuvant chemotherapy compared with 18 children treated with radiotherapy or amputation only.

OSTEOGENIC SARCOMA

Osteogenic sarcoma is another rare but highly malignant tumour of bone which while it remains relatively localized at the primary site (usually at the end of the femur or tibia) nevertheless sends metastases to the lungs at an early stage. These metastases appear on chest radiographs six months or more after diagnosis. Previously the only effective treatment was radiotherapy to the primary site followed by amputation, giving a cure rate of only 20%. In the last few years combination chemotherapy with vincristine and cyclophosphamide has produced temporary responses when metastases were present. Some definite regressions also occurred when children were treated with large doses of methotrexate followed by folinic acid to prevent the severe toxic side effects of the methotrexate. Several groups of doctors are now reporting success using adjuvant chemotherapy including cyclophosphamide, vincristine, adriamycin, melphalan, and high doses of methotrexate and folinic acid rescue. This chemotherapy, which is intended to destroy micrometastases, is started shortly after amputation. Using this method, Sutow *et al.*⁷ now report 10 out of 18 children alive and well with no evidence of pulmonary metastases 15 months from diagnosis. Great care is needed in the control of this therapy but two patients under our care at present are tolerating a similar regimen without undue toxicity.

Conclusions

This brief survey of the present position of therapy in some of the common childhood malignancies must conclude with a strong note of warning of the toxic side effects of these agents, which are listed in table II.

The chemotherapeutic agents used and their quantity depend on the tumour, the clinical state of the child and its age, the stage of the tumour, and the state of liver and renal function. The chemotherapist has to weigh these factors before he prescribes; for this reason no dosage has been given.

TABLE II—Toxicity of Some Cancer Chemotherapy Drugs

Drugs	Toxicity
Adriamycin	Marrow toxicity, cardiotoxicity, hepatotoxicity, alopecia
Cyclophosphamide	Marrow toxicity, haemorrhagic cystitis, alopecia
Dactinomycin	Gastrointestinal disturbance, marrow toxicity, sensitisation to radiotherapy
Methotrexate	Marrow toxicity, gastrointestinal toxicity, hepatotoxicity
Nitrogen mustard	Marrow toxicity, nausea, vomiting, local vesicant action
Prednisolone	Salt and water retention, hypertension, diabetes
Vincristine	Neurotoxicity, marrow toxicity, inappropriate antidiuretic hormone syndrome

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Any Questions?

We publish below a selection of questions and answers of general interest

Steroids in Acute Ischaemic Heart Block

What is the present status of steroids and/or A.C.T.H. in the treatment of acute heart block complicating myocardial infarction?

Though benefit has been reported after the use of steroids or A.C.T.H. in the acute ischaemic block^{1,2} this treatment has been superseded by temporary pacemaking or a controlled intravenous infusion of isoprenaline.³ Conduction may return after the use of steroids but the effect is not predictable and cannot be adjusted on a moment to moment basis in the same way as can be done with isoprenaline. Not all patients with acute block during myocardial infarction will need treatment for this arrhythmia but where this is indicated temporary pacing is the method of choice.⁴

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Halitosis

The career of a dental student is in jeopardy because of persistent severe halitosis, despite the use of chlorophyll and toothpaste. Investigations have shown no obvious cause. What can be done?

Poor oral hygiene or periodontal diseases are the commonest causes of halitosis. Bad breath may arise after ingestion of certain foods, drinks, or drugs, or from pathological conditions in the mouth, the nasopharynx (e.g., sinusitis, septic adenoids or tonsils, pharyngitis, and other respiratory infections), in the lungs or bronchi (e.g., bronchiectasis, lung abscesses) and very occasionally from gross disease of the stomach and oesophagus and in severe acute liver failure or chronic renal failure. The characteristic odour of ketones in a diabetic crisis is well recognized.

Deposits of calculus on the teeth may aggravate halitosis. The source of the smell is usually putrefying food debris, pus, or exudations, or blood from ulcers within the mouth. As periodontal disease advances and the soft tissues and bone supporting the teeth recede, debris collects very rapidly between or around the teeth and is difficult to remove by brushing the teeth. Exudation of pus from the ulcerated areas in periodontal pockets also make the condition worse. Any

ulcer or tumour within the mouth may cause bad breath and in the case of acute ulcerative gingivitis is accompanied by a characteristic and easily recognizable odour.

After acute ulcerative gingivitis it is often difficult to prevent the condition relapsing into a chronic phase, especially under flaps over partially erupted impacted teeth and, in this age group, especially over wisdom teeth. Misplaced erupted teeth often create areas where food can impact and can only be dislodged with difficulty and where gingival disease is common. Large open carious cavities, badly contoured fillings, and ill-fitting dentures may all harbour food debris. Open sinuses associated with dead teeth or infected cysts may discharge pus into the mouth. Mouth breathing or snoring cause dryness of parts of the mouth and accelerate putrefaction of food debris. Certain foods, drinks, and drugs are well recognized as causing bad breath.

Mumps Vaccination

Has vaccination against mumps using a live virus proved to be helpful in preventing attacks?

Vaccination against mumps was included in routine childhood immunization programmes in the United States soon after licensure of the Jeryl Lynn strain live attenuated mumps virus vaccine in 1967. In Britain the vaccine became commercially available about two years ago but no recommendation concerning its use in routine immunization programmes has been issued by the Department of Health. The Jeryl Lynn strain vaccine produces mumps neutralizing antibody in over 95% of mumps-susceptible subjects.¹ Though the level of antibody is considerably lower than observed after natural infection¹ its pattern of persistence closely parallels that of natural mumps neutralizing antibody.² A mumps neutralizing antibody titre of 1:1 or over is regarded as protective³ and since antibody induced by the vaccine is persistent vaccination is expected to provide solid immunity. This is supported by an observation⁴ that 27 schoolchildren exposed to natural infection five years after vaccination did not develop the disease whereas 44 of the 59 unvaccinated children at the school had mumps.

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