The Effect of Treatment on Lymphomas and Childhood Solid Tumours

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A number of malignant conditions have shown an improved response to therapy in the last decade, and the lymphomas, particularly Hodgkin's disease and some of the childhood malignancies, are good examples. The improvement in response rate has been accompanied by an increase in the time during which patients are free from all evidence of disease and, with increasing duration of the disease-free interval, an increase in long-term survival and possible cure has been apparent.

The results of treating Hodgkin's disease in its early stages with radiotherapy are excellent. Peters (1950) and subsequently many others (Hynes, 1955; Peters and Middlemiss, 1958; Easson and Russell, 1963) showed that it was possible to cure Hodgkin's disease by radiotherapy during the period when it was localised. In disseminated disease the introduction of combinations of four effective agents given intermittently has resulted not only in a great improvement in the response rate but also in a considerable increase in the duration of survival (De Vita et al., 1970). Nitrogen mustard, vinblastine, procarbazine and prednisolone (Nicholson et al., 1970) produce a response rate of 84 per cent in previously untreated patients. If the survival of these patients is compared with a similar group of patients with Hodgkin's disease treated with a single agent only for a few years before the introduction of quadruple chemotherapy it can be shown that there is a marked difference in survival (Fig. 1). The survival curve for the patients treated with single drugs only is no better than that seen in patients treated with palliative radiotherapy 40 years previously, reported by Craft (1940).

A marked change in the natural history of Hodgkin's disease in children has also been seen following the introduction of combination therapy for those children with disseminated disease. It has been policy at St Bartholomew's Hospital for the last four years to treat all children with disseminated disease with quadruple therapy. This has been well tolerated and a comparison with the previous experience using single agents only emphasises that it has been well worth while (Fig. 2).

In correctly staged patients, groups of effective drugs given intermittently to avoid excessive toxicity increase the rate of remission, the duration of complete remission, and survival.

Non-Hodgkin lymphoma includes a variety of malignancies of lymphoid tissue
Fig. 1. Survival in disseminated Hodgkin's disease. Single versus multiple drug therapy of adult patients.
for which there is no generally agreed classification. Improvements are being made in the classification (Lukes and Collins, 1975) and it is generally agreed that in children these highly malignant tumours nearly always diffusely involve the lymph nodes, and the lymphoid cells are blastic in character. If the tumours present locally in the lymphoid system they soon spread to involve the bone marrow, blood and central nervous system (Watanabe et al., 1973; Garwicz et al., 1974; Pinkel et al., 1975). The improvement that has occurred in the prognosis is due to a better understanding of the pathology and natural history. The treatment of

Fig. 2. Survival in disseminated Hodgkin's disease. Single versus multiple drug therapy of children.
local disease by surgery, radiotherapy or palliation with single agents has given way to the idea that the disease should be regarded as similar to acute leukaemia with the difference that aggregation of malignant lymphatic tissue has occurred (Aur et al., 1971). With the exception of children with very localised disease usually involving the cervical glands (Pinkel et al., 1975) all series have shown a median survival of only a few months and very few long-term survivors.

In the past three years all children with this diagnosis have been treated at St Bartholomew's Hospital with an intensive induction regime of vincristine, prednisolone, adriamycin and asparaginase. When they have achieved complete remission they have had cranial irradiation and intrathecal methotrexate as prophylaxis against central nervous system relapse and then have been maintained on cyclophosphamide, methotrexate and 6-mercaptopurine. In a small series of six children treated in this manner four are alive, three in continuous complete remission, compared with only one child in 20 treated with local radiotherapy and single agents (Fig. 3).

Although there appears to be a considerable change in the natural history of this disease when this form of treatment is used, great caution is required with regard to long-term survival. If this condition behaves similarly to acute leukaemia these patients are at risk of relapse for many years ahead, and if relapse occurs in the bone marrow it carries the same hopeless prognosis that it does in acute lymphoblastic leukaemia.

In the last few years there has been a considerable improvement in the outlook in acute lymphoblastic leukaemia, with some centres reporting a 50 per cent five-year survival rate (Pinkel et al., 1972). There has been an equally satisfactory improvement in some solid tumours of childhood, and a few of these tumours in which results are striking and in which the treatment illustrates principles that might be successfully applied to adult tumours will now be considered.

Wilms' tumour or nephroblastoma, a renal malignancy usually found in very young children, has shown a steadily improving cure rate over the years as the importance of correct staging, the combination of surgery and radiotherapy and, more recently, the addition of adjuvant chemotherapy has been realised. This steady improvement is shown in Fig. 4 which is taken from the National Cancer Institute Survey of cases presenting between 1940 and 1965 (Everson and Fraumeni, 1975).

Recent reports from the National Wilms' Tumour Study Group in the U.S.A. suggest that, when vincristine and actinomycin D are given prophylactically following surgical removal of tumour and radiotherapy to the renal bed in those children with early disease who are suitable for irradiation, an 80 per cent cure rate is possible.

The outlook in disseminated disease when metastatic spread has occurred in the lungs and elsewhere has inevitably been bad. No children survived in a large series reported by Jereb and Eklund (1973), and our own experience has shown a survival of only 8 children out of 40 with Stage III or IV disease. We are
presently trying to improve this by combining irradiation with a four-drug intermittent intensive regime using actinomycin D, vincristine, adriamycin and cyclophosphamide. So far, six out of seven children treated with this regime have responded completely and there would appear to be a significant improvement in disease-free survival.

Rhabdomyosarcoma is the commonest of the soft tissue sarcomas of children and chiefly affects the head and neck or genito-urinary tract. Studies done in United States centres where these diseases were concentrated showed some 10 years ago (Pratt, 1969) that these tumours were more sensitive to radiotherapy.
and chemotherapy than had hitherto been thought. Recently, good results have been reported in children even where these tumours have been inaccessible to surgery, such as those of the head and neck (Donaldson et al., 1973). Intensive therapy combining irradiation with intermittent combinations of effective drugs has shown a good outcome in two-thirds of those children with apparently local or regional disease. Many deaths occurred previously from this tumour, not because of failure to control the primary tumour but because small metastatic deposits, unrecognisable either clinically or radiologically, were present at the time of presentation and still remained viable after treatment. These so-called micrometastases present a unique opportunity for successful chemotherapy and should respond to combinations of drugs given intermittently. The principle of adequate control of the primary tumour with elimination of micrometastases has been successfully applied to a number of childhood tumours.

Eleven children, mostly with regional rhabdomyosarcoma involving the head and neck, orbit or pelvis, have been treated with radiotherapy and at the same time have had vincristine, cyclophosphamide and actinomycin D. It is not possible to go into details of management but such procedures as ‘second look’ surgery and modification of the drug regimes with deletion of one drug and addition of another, such as adriamycin, may be required occasionally.

Fig. 4. Progressive improvement of survival in Wilms’ tumour. (Courtesy Editor Medical and Pediatric Oncology.)

NCI. Survey 1975.
Using this therapy, and comparing our results with a similar group of children treated previously by surgery and radiotherapy and occasional single agents, there is no doubt that a very definite change has been induced in the natural course of events (Fig. 5).

Continual reference has been made throughout this account to historical control groups. In uncommon tumours such as those affecting children this is inevitable. Confirmatory evidence of randomised studies offers, of course, more secure foundation for advocating any particular line of treatment. In rhabdomyo-

Fig. 5. Survival of children with rhabdomyosarcoma treated with radiotherapy and adjuvant chemotherapy compared with patients treated with surgery or radiotherapy only. (Courtesy Editor British Medical Journal.)
sarcoma such a study is available. Children’s Cancer Group A, in which 81 children were evaluable, contained a small group of 15 children who received irradiation but no chemotherapy; 8 of these children (53 per cent) developed local recurrence or metastases compared with only 3 of 17 children who received chemotherapy in addition (18 per cent). This was significant at the 5 per cent level (Heyn, 1974).

This successful multimodal therapy has been applied to other sarcomas, notably Ewing’s sarcoma of bone which has had a disappointing cure rate of less than 10 per cent for many years. The improvement that has occurred has been due to a better control of the primary bony lesion with intensive radiotherapy employing doses ranging from 5,000 to 6,000 rads (Hustu et al., 1972; Rosen et al., 1974) and the treatment of micrometastases with combinations of two or more agents. In 16 patients treated with radiotherapy and actinomycin D, adriamycin, vincristine and cyclophosphamide adjuvant chemotherapy, Rosen et al. (1975) have 12 patients in complete remission between 12 and 52 months. Our own experience in a small group of four patients treated with vincristine, adriamycin and cyclophosphamide adjuvant chemotherapy is similarly encouraging (Fig. 6).

Finally, there is osteogenic sarcoma, one of the most lethal of all tumours, especially when it occurs in children. A number of series that have included both children and young adults in which primary treatment has been surgical or radiotherapeutic have given five-year survival rates varying between 10 and just over 20 per cent (Marcove et al., 1970; Cade, 1955). The natural history of this malignancy shows a relentless appearance of pulmonary metastatic deposits with an approximate rate of appearance of 10 per cent per month following amputation of the primary tumour. As soon as metastases appear death has been inevitable in a few months (Marcove et al., 1970). In series in which only children with classical osteogenic sarcoma have been included survival is almost unknown. It would appear that the treatment advocated by Cade (1955), first using radiotherapy in an attempt to control primary disease and then proceeding to amputation if pulmonary metastases do not appear, is unlikely to be successful. Radiotherapy even in very high doses is not successful in dealing with the primary tumour and micrometastatic deposits are present elsewhere at an early stage.

Cyclophosphamide, high dose methotrexate with citrovorum factor rescue and adriamycin have been found to be effective on occasions against established metastases. Used singly or in combination these agents have proved effective in preventing the development of metastases. Table 1 is taken from a review by Jaffe (1975) of the treatment of bone tumours and includes results from most of the major centres. It can be seen that nearly 80 per cent of the patients have no evidence of spread of disease after treatment from two to 37 months. This kind of result would have been inconceivable a few years ago. It has not been achieved without some loss of life during treatment as these combinations are extremely toxic and should only be given in special centres able to deal with acute and
chronic complications of therapy. With care, the results are very rewarding and we have one child who is alive and with no evidence of disease at more than a year.

It is necessary to end with a note of caution on the adverse effects that may occur. It is certainly the responsibility of all centres engaged in these treatments to monitor long-term adverse effects, especially in children.
Table 1. Treatment of osteogenic sarcoma (after Jaffe, 1975)

| Institute (Author)                          | Chemotherapy                | No. of patients | No. NED* | Months duration (median) |
|---------------------------------------------|-----------------------------|-----------------|----------|-------------------------|
| S.W. Oncology Group (Sutow)                 | CONPADRI I                  | 38              | 24†      | 3.37 (18)               |
|                                             | COMPADRI II†                | 14              | 13       | 2.11 (6)                |
| Sidney Farber Cancer Center (Jaffe)         | MTX→CF                     | 18              | 16       | 2.22 (8)                |
| Acute Leukaemia Group B (Cortes and Holland)| Adriamycin                  | 21              | 16       | 1.30 (10)               |
| Children’s Hospital at Stanford (Wilbur)    | MTX→CF                     | 6               | 5        | 3.15 (4)                |
|                                             | Cyclophosphamide            |                 |          |                         |
|                                             | Adriamycin                  |                 |          |                         |
| St Jude Children’s Hospital (Pratt)         | MTX→CF                     | 7               | 6        | 2.15 (8)                |
|                                             | Cyclophosphamide            |                 |          |                         |
|                                             | Adriamycin                  |                 |          |                         |
| Memorial Hospital (Rosen)                   | MTX→CF                     | 11§             | 9        | 2.22 (7)                |
|                                             | Cyclophosphamide            |                 |          |                         |
|                                             | Adriamycin (T-4)            |                 |          |                         |
| Total                                       |                             | 115             | 89 (78%) |                         |

* No evidence of disease
† 10 patients have been followed for greater than 20 months
‡ MTX→CF added to CONPADRI I
§ Includes 5 patients starting adjuvant therapy after surgical removal of pulmonary metastases

In summary, the current improvement in results in childhood malignancies and in the lymphomas comes from a more precise and accurate assessment of histology and staging of the disease, better control of the primary lesion and more effective treatment of metastatic disease. The application of these principles to adult solid tumours will, one hopes, give rise to equally encouraging results.

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GROWING OLD GRACEFULLY
A physician who is advancing in years, yet unconscious of any decay in his faculties, may occasionally experience some change in the wonted confidence of his friends. It behoves him to admit this change without dissatisfaction or fastidiousness, regarding it as no mark of disrespect. The commencement of the period of senescence, when it becomes incumbent on a physician to decline the offices of his profession, is not easy to ascertain; and the decision on so nice a point must be left to the moral discretion of the individual. As age advances, therefore, a physician should, from time to time, scrutinise impartially, the state of his faculties; that he may determine, bona fide, the precise degree in which he is qualified to execute the active and multifarious offices of his profession. And whenever he becomes conscious that his memory presents to him, with faintness, those analogies, on which medical reasoning and the treatment of diseases are founded; that diffidence of the measures to be pursued perplexes his judgment; that, from a deficiency in the acuteness of his senses, he finds himself less able to distinguish signs, or to prognosticate events; he should at once resolve to retire from the engagement of business.
(Extracted from the writings of Dr Thomas Percival (1740-1804).)