PAPERS AND ORIGINALS

Radiotherapy and adjuvant combination chemotherapy for childhood rhabdomyosarcoma

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Summary

The treatment of children with rhabdomyosarcoma by a combination of surgery, radiotherapy, and chemotherapy has resulted in an improved disease-free survival time. Of 11 children with regional disease eight (72%) remained well, with no evidence of disease, four to 36 months after diagnosis. Chemotherapy for one year with vincristine, actinomycin D, and cyclophosphamide was well tolerated during and after radical radiotherapy and surgery. The natural history of this malignancy has been altered in these patients when compared with that in a historical group of 17 children, only two of whom remain alive. There has been no serious short-term toxicity so far.

Introduction

The commonest soft-tissue sarcomas in childhood are undifferentiated, embryonal, or, less commonly, alveolar rhabdomyosarcomas. It used to be assumed that these tumours did not respond to treatment by radiotherapy or chemotherapy, but several studies have shown that localised and even extensive regional disease in surgically inaccessible sites can be treated and responds to radiotherapy and chemotherapy in combination. Pratt¹ showed that radiotherapy to the primary site together with adjuvant vincristine, actinomycin D, and cyclophosphamide given over a period could improve the median duration of survival. Donaldson *et al*² showed that this could be done in rhabdomyosarcoma of the head and neck and achieved a remarkable two-year survival of 74%. Recently Heyn *et al*,³

using radiotherapy with vincristine and actinomycin D, have achieved a two-year survival of 85.7% in tumours occurring at all sites. This is a remarkable improvement on the average 5% survival seen when surgery alone was used. Some scepticism has been shown about the addition of chemotherapy, however, especially in Britain, where its contribution has been questioned.⁴

We have undertaken a programme of careful staging of the tumour followed by radiotherapy to the primary site and regional extensions, accompanied by three-drug adjuvant chemotherapy using vincristine, actinomycin D, and cyclophosphamide continuously for 12 months. When one of these drugs could not be administered owing to toxicity we replaced it with adriamycin. We report here the response rate, survival, and toxicity and compare survival with that in a historical group of children with rhabdomyosarcomas treated with surgery and radiotherapy only.

Patients and methods

Eleven consecutive patients with regional rhabdomyosarcoma were treated. They included one patient with orbital disease in whom we suspected extension; this was later confirmed when she was shown to have stage IIA disease. There were no exclusions. Before treatment a full clinical examination was performed. The biopsy material of referred patients was reviewed and if equivocal a further biopsy was done; the material was taken into glutaraldehyde for examination by electron microscope. Whenever possible the material was stained with periodic acid-Schiff stain, which, if positive, provides useful confirmatory evidence of rhabdomyosarcoma. When the rhabdomyosarcoma was histologically confirmed the following investigations were performed: full blood count, estimation of urea and electrolytes, liver function tests, bone marrow examination, chest x-ray examination, intravenous pyelography (when indicated), ⁹⁹Tc bone scan with a gamma-camera, and electrocardiography. On the basis of these findings the tumours were staged as follows: stage I—localised disease; stage II—regional disease: IIA completely resectable, and IIB non-resectable or only partially resectable; stage III—generalised disease: IIIA distant metastases with normal bone marrow, and IIIB distant metastases with marrow containing rhabdomyoblasts. We are concerned in this report only with children with stage IIA and IIB disease. Treatment consisted of irradiation, and completion of radiotherapy admitted the child for assessment.

Radiotherapy—Treatment consisted of radiotherapy to generous volumes including the primary tumour, its local extensions, and

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regional lymphatic drainage. Tumour doses of 4000-6000 rads were given depending on site, volume, critical organs, and the patient's age, using a TEM Stabilatron Telecobalt Unit. Orbital tumour volumes were treated at 1000 rads/week and the larger chest, abdominal, or pelvic volumes at 600-800 rads/week. The youngest children with orbital tumours required ketamine general anaesthesia and were treated three times a week; otherwise daily treatment was given five times a week. With large tumours a one to two-week rest was usually dictated by skin, mucosal, or systemic reactions after three or four weeks of treatment. In some children with very extensive tumours radiotherapy was deferred until the response to several courses of chemotherapy had been assessed.

Chemotherapy—At the same time chemotherapy was started with vincristine 1.5 mg/m²/week, actinomycin D 0.6 mg/m²/week, and cyclophosphamide 300 mg/m²/week. If the blood count allowed this was continued for six courses, after which chemotherapy was spaced out to intervals of two weeks or more depending on the condition of the patient. Often both radiotherapy and chemotherapy were interrupted through the initial period of treatment.

Surgery—When necessary residual disease was removed surgically after radiotherapy and chemotherapy.

The treatment schedule is given in fig 1.

FIG 1—Schedule for combination therapy of childhood rhabdomyosarcoma.

Results

Eleven children have been treated so far (see table). Nearly all children had regional disease with either the site or extent of the disease precluding surgical removal. As we have gained more experience it has become evident that extensive surgical procedures initially are inadvisable. Surgery has been used only to remove residual tumour, and we have often found that no viable tumour remains in the residuum. The sites of tumour have been those common for rhabdomyosarcoma: the head and neck, particularly the orbit, and the genitourinary tract. The two largest tumours were one in the right lung, where it almost filled the right pleural cavity, and one in the pelvis, where a mass was palpable above the umbilicus. In spite of the size and site every tumour responded completely—that is, the child returned to normal health with no symptoms referable to the tumour and there was no clinical or radiological evidence of tumour. In those children who underwent a second operation no viable tumour was evident.

Survival—The survival of these 11 children was compared with the survival of a historical group of 17 children treated with surgery and radiotherapy only. The historical group consisted of three patients with stage I tumours, four with stage IIA tumours, and 10 with stage IIB tumours. The survival of both groups of patients, plotted on a log scale, is shown in fig 2. The median survival of the 17 patients

FIG 2—Survival of children with regional rhabdomyosarcoma using surgery and radiotherapy (DXT) only and surgery, DXT, and chemotherapy. Circles represent individual survival times in the eight children still alive.

previously treated was 10 months, whereas the median has not been approached by the present group. Although the ultimate cure rate cannot be assessed the increased disease-free survival should indicate an improved cure rate; certainly the natural history of this condition has been profoundly changed. We believe this has been achieved by the addition of chemotherapy. It is relevant that in the three children who relapsed and died the relapse occurred at the primary site in two and intracerebrally in the third (case 5), where presumably the chemotherapy had been unable to achieve an effect.

Modifications to treatment—Two children (cases 2 and 6) developed side effects from vincristine and were therefore given adriamycin to a total of 234 mg and 180 mg—doses well within the cardiotoxic limits for this drug. The regimen was well tolerated but two children were unable to finish a full year of treatment. One patient (case 6) had extensive radiotherapy and a persistently low blood count so that treatment was stopped after seven months, and another (case 3) had no further chemotherapy when "second look" surgery—exenteration of the orbit—showed no evidence of viable tumour. In case 8 there was a massive intrathoracic rhabdomyosarcoma which initially decreased in size with radiotherapy and adjuvant chemotherapy; it seemed to respond only slowly, however, and apparent residual disease was resected. Serial sections of the specimen showed no viable tumour. Chemotherapy was continued without ill effects for a full year after removal of the tumour.

A total of 167 courses of treatment have been given; 38 courses were delayed—13 owing to intercurrent infection (upper respiratory tract infection, chicken pox, etc); four owing to low blood counts; five owing to anorexia or nausea; two owing to radiotherapy reaction, including radiation colitis in case 6; and the remainder owing to rashes. The protocol was on the whole well tolerated; 94% of the dose of vincristine required by the protocol, 72% of the dose of actinomycin D, and 76% of the dose of cyclophosphamide were given. Liver function tests, including estimations of bromosulphthalein excretion, and cardiac function tests, including echocardiography done at the end of the courses, showed no abnormalities.

Details of patients and outcome of combination therapy

Case No	Age	Sex	Stage	Primary site	Response	Duration of survival (months)
1	3	F	IIA	Orbit	Complete	29 NED
2	6	M	IIA	Parastesticular	Complete	36 NED
3	5	F	IIA	Orbit	Complete*	29 NED
4	2	M	IIB	Orbit	Complete	16 DWD
5	2	F	IIB	Orbit	Complete	15 DWD
6	1½	M	IIB	Pelvis	Complete*	28 NED
7	1 month	M	IIB	Parastesticular	Complete*	26 DWD
8	8	M	IIB	Intrathoracic	Complete*	13 NED
9	1½	M	IIB	Larynx	Complete	13 NED
10	2	F	IIB	Mandible	Complete	7 NED
11	4	M	IIA	Parastesticular	Complete	4 NED

*Second-look surgery.

NED = No evidence of disease. EWD = Died with disease.

Discussion

The combination of surgery, radiotherapy, and chemotherapy used in this study to treat children with stage IIA and IIB rhabdomyosarcoma has been successful in modifying the course of the disease. Eight out of 11 children were alive four to 36 months after diagnosis compared with only two out of 17 children in a group previously treated with surgery and radiotherapy. The improvement shown in this study is probably due to chemotherapy and, possibly, more extensive radiotherapy and is of the same order as that described by others.^{2 3 5 6} These findings confirm our initial report on this particular schedule of drugs.⁷ We presume that the improved outcome was due to the elimination of micrometastatic disease present at the initia

appearance of the tumour but undetectable clinically. It may be argued that the improved outlook has only been shown in serial studies using historical controls and other factors such as staging and more intensive radiotherapy might be producing these results. But the improvement was so considerable that this is hardly likely. Furthermore, in a study by the Children's Cancer Study Group A³ of 15 children treated by radiotherapy alone eight developed local recurrence or metastases compared with only three out of 17 children concurrently treated by radiotherapy and chemotherapy. This result was significant at the 5% level.

The chemotherapy used in this study has not produced any deaths and no undue short- or long-term toxicity. The best regimen, in terms of number of drugs, doses needed, and length of adjuvant therapy, is not yet known. Our regimen is less intense than some reported, yet it appears to give satisfactory results. Co-ordinated studies between centres will be important,

especially in view of the implications of these results for the treatment of the commoner adult solid tumours.

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Short ACTH test in assessing hypothalamic-pituitary-adrenocortical function

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Summary

The adrenocortical response to the simple 30-minute ACTH stimulation test was compared with the hypothalamic-pituitary-adrenocortical (HPA) response to insulin-induced hypoglycaemia in 25 patients with various degrees of hypothalamic-pituitary malfunction. The correlations between the increase in plasma cortisol during insulin hypoglycaemia and that during ACTH stimulation ($r=0.66$) and between peak plasma cortisol levels during the two tests ($r=0.90$) were highly significant. Peak plasma cortisol levels in individual patients were similar on both tests, no patient showing any major discrepancy between the two test results. Thus the simple 30-minute ACTH stimulation test seems to be reliable in detecting impaired HPA function.

Introduction

Integrated hypothalamic-pituitary-adrenocortical (HPA) function is usually assessed by the insulin-induced hypoglycaemia test, whose clinical value has been clearly shown.^{1,2} This test, however, is uncomfortable for the patient and requires strict supervision of him throughout the test. Theoretically the simple 30-minute ACTH stimulation test, easy to perform and without discomfort to the patient, tests only adrenocortical function and not the integrated HPA function. We have shown, however, that

the 30-minute ACTH stimulation test reliably predicts the integrated HPA response to surgical stress in patients treated with glucocorticoids.³ We therefore compared the adrenocortical response to ACTH with the HPA response to insulin-induced hypoglycaemia in patients with various degrees of hypothalamic-pituitary malfunction.

Patients and methods

Twenty-five patients were investigated (see table). Fourteen (cases 1-14) had undergone hypophysectomy because of pituitary adenoma or cyst, and eight of these patients (cases 1-8) were on glucocorticoid substitution treatment with 25 or 37.5 mg of cortisone acetate daily. Three patients (cases 15-17) had had a pituitary tumour diagnosed but had not yet been subjected to surgery. One patient (case 18) had galactorrhoea but no evidence of hypothalamic-pituitary tumour, and the remaining seven patients (cases 19-25) had various symptoms that made us suspect hypothalamic-pituitary disease. Clinical investigations, however, including neurological and ophthalmological examination, pneumoencephalography, EMI brain-scan, and electroencephalography, showed no evidence of hypothalamic-pituitary disease. Furthermore, secretion of growth hormone (peak plasma value during hypoglycaemia or arginine infusion, or both, 6.2-24 $\mu\text{g/l}$) and thyroid and gonadal function were normal in these eight patients (cases 18-25). None of the patients had hyperpigmentation or electrolyte disturbances. In the eight patients receiving glucocorticoid substitution treatment the last dose was given the evening before the study. All patients gave their informed consent.

On the day of the examination the patients were fasting, and an insulin hypoglycaemia test was begun between 10 and 11 am by giving crystalline insulin 0.15 IU/kg body weight intravenously. Blood for cortisol and glucose analysis was drawn from an intravenous cannula 10 minutes before and at the insulin injection and 30, 45, 60, 75, and 90 minutes after the injection. The test was considered adequate only if blood sugar fell to at least 2 mmol/l (36 mg/100 ml) and the patient sweated. In some patients a higher dose of insulin was used to achieve these conditions. On the same day between 3 and 4 pm an ACTH stimulation test was performed by injecting 250 μg of α^{1-24} ACTH (tetracosactrin) intravenously. Blood for cortisol determination was drawn immediately before and 30 minutes after ACTH injection.

Blood glucose was measured by a glucose oxidase method and plasma cortisol fluorimetrically as 11-hydroxycorticosteroids.⁴

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