ACTINOMYCIN D IN WILMS' TUMOUR: TREATMENT OF LUNG METASTASES*

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This paper discusses recent world trends in the treatment of Wilms' tumour, particularly as exemplified by their impact on practice at the Royal Children's Hospital, Melbourne.

Following the use of actinomycin D in the therapy of lung metastases of Wilms' tumour (see below), it became apparent that this drug was able, at times, to inhibit their growth and, more rarely, to cause their complete regression.

In order to examine the merits of putting the drug to more general use in the treatment of this malignancy, a meeting of those interested was held at the Royal Children's Hospital on April 15, 1959.

Examination of records indicated that, since the introduction of post-operative irradiation of the tumour bed, death from Wilms' tumour was largely the result of blood-stream dissemination. Nevertheless, as adduced by the author in 1957, in a review of 26 consecutive cases, the recovery rate was still only 11.5%.

In view of the proved effect of actinomycin D on established lung metastases it was considered that if nephrectomy were performed under its cover haematogenous dissemination might be eliminated and any minimal undetectable metastases already present be suppressed.

Accordingly the following three decisions were taken.

(1) That actinomycin D be introduced into the treatment sequence; (2) that the drug be pushed to the limits of tolerance; and (3) that tumour bed irradiation be deferred for a limited period in order to avoid the simultaneous action of two bone marrow depressants.

The following plan was conceived and enunciated in terms of days of treatment.

Actinomycin D was administered in a total dosage of 120 μ g./kg., divided into 8 equal injections to be

given on Days 1, 2, 3, 4, 5, 7, 9, and 12. Nephrectomy was performed on Day 3.

Irradiation was commenced on Day 26 and continued daily to a dosage of 3,000 rads delivered over approximately 28 days.

The results of a series of 18 consecutive cases treated thus are here recorded and annotated in the accompanying Table. 11 of the 18 have survived without evidence of recurrence for periods of from 24 to 58 months—a recovery rate of 62% with a minimum survival time of 2 years.

TABLE

Place in Series	Age at Time of Nephrectomy (mth.)	Sex	Result	Survival from Time of Nephrectomy (mth.)
1	12	F	Dead	7
2	10	M	Alive	58
3	36	M	Dead	13
4	16	F	Alive	57
5	36	M	Dead	15
6	17	M	Alive	41
7	60	F	Dead	6
8	13	M	Alive	41
9	84	F	Dead	4
10	46	F	Alive	40
11	42	F	Alive	40
12	27	F	Alive	35
13	42	F	Alive	29
14	3	M	Alive	28
15	39	F	Alive	28
16	33	F	Alive	27
17	44	M	Dead	7
18	15	F	Dead	0.25

While one realizes that these patients are not yet assured of ultimate recovery it is still true to say that the usual experience of Wilms' tumour is that cases remaining completely well for 2 years after nephrectomy are likely to be permanent cures. The comparison with the previous recovery rate of 11.5%, recorded in 1957, is striking. Of the 7 deaths, 2 were cases of most unfavourable initial prognosis in so far as metastases were present before the start of treatment (in one case involving the liver, in the other the scalp) and a third died on the sixth post-operative day from septicaemia. The remaining 4

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pursued a course that appeared to be uninfluenced by actinomycin D.

The only significant change in the treatment used in the present series has been the introduction of actinomycin D, and it is concluded that this drug is responsible for the improvement in results.

Toxic Effects of Actinomycin D

Actinomycin D is a toxic antibiotic that appears to have a selective effect on Wilms' tumour.

The toxic effects are manifest in relation to (a) the bone marrow, where the activity is depressed even to the point of aplastic anaemia; (b) the skin and its appendages, causing macular rashes and epilation of the hair of the scalp; and (c) the gastro-intestinal tract, as instanced by anorexia, vomiting, ulcerative stomatitis, and diarrhoea (often blood-stained).

There have been two instances (Case 15 and a subsequent case too recent for inclusion in this series) of the development, 2 weeks after cessation of radiotherapy, of oedema of the extremities and ascites with marked liver and splenic enlargement: in both the tumour was in the right kidney. It is suggested that the effect of irradiation on the liver was potentiated by the previous action of actinomycin D with resultant swelling and portal obstruction. Investigations on Case 15 showed that there was no obstruction of inferior vena cava or hepatic veins (as determined by catheterization) but that the serum protein level had fallen to 5 g./100 ml., with decrease in the albumin fraction, accounting for the generalized oedema. The ascitic fluid was milky in appearance but proved unsatisfactory for cell examination owing to precipitation of lipid material. The second case (a recent one) presented a similar picture. Both recovered on supportive treatment only, liver and spleen returning to normal size over a period of 4 months.

In an even more recent case (still undergoing irradiation), on the eighth day after starting treatment, acute intussusception occurred in the lower ileum, demanding bowel resection. The bowel in the region of the apex of the intussusception displayed several swollen areas with central ulceration. Though specific pathological proof is lacking, it seems logical to place this occurrence in sequence with the well-known manifestation of blood-stained diarrhoea, and to class it as a further complication, hitherto unlisted, of actinomycin D administration (the child also exhibited skin lesions and stomatitis). The findings, recorded by Philips, Schwartz, Sternberg, and Tan in 1960, of extensive damage to small and large intestines of rats, with swelling of cells and submucosal oedema and congestion as a result of actinomycin D therapy, are an indication of

what could occur in the human and could well be the basis of an intussusception.

It should be noted that toxic features may vary in nature and in degree from patient to patient and perhaps from one batch of actinomycin D to another. Treatment must be carefully monitored by both clinical and laboratory observations. Though no modification of dosage was necessary in any of the cases recorded here, in two recent cases it was thought wise to omit the final dose.

Management of Established Lung Metastases

Cases of established lung metastases may be divided into two categories according to whether actinomycin D has or has not previously been administered.

Cases in the first category (i.e. in which actinomycin D has previously been administered) are in our experience resistant to further actinomycin D and should be treated initially by irradiation, supplemented by a modified course of actinomycin D (this combination is recommended in view of the probable potentiation of the effect of irradiation by the drug as suggested by D'Angio, Farber, and Maddock (1959), and by Farber, D'Angio, Evans, and Mitus (1960)). If these measures fail to procure radiographic disappearance of metastases, or if initial regression is not maintained, operative measures should be instituted unless the dissemination is obviously too extensive to attempt salvage. Other chemotherapeutic agents may be of use as adjuncts to operation, but our experience of these is inadequate to form a definitive opinion of their value.

Cases in the second category should be given initially a full course of actinomycin D (see above). Anything short of complete radiographic regression is an indication for irradiation. Thereafter management is along similar lines to those of the first category.

Surgical extirpation may be by wedge resection, segmental resection, lobectomy, or perhaps, pneumonectomy. Segmental resection or lobectomy is the procedure of choice if warranted by a favourable distribution of metastases. Numerous scattered deposits may indicate multiple wedge resections or, if limited to one lung, perhaps pneumonectomy. Bilateral deposits are not *per se* a contraindication to operation.

Seven cases have been operated on for lung metastases: 3 are still alive and free from metastases and have now been well for periods of from 4½ to 5 years. The fourth, and the sole case in which pneumonectomy was performed, died 6 months after this operation from liver secondaries. The fifth died of nephritis 4 years after bilateral wedge resection,

and necropsy revealed no evidence of malignancy. The sixth died from a solitary cerebral metastasis with no other malignant deposits detectable at necropsy, and the seventh succumbed to his pulmonary metastases.

The first case treated along these lines is noted in some detail as an example of the routine adopted: V.C., a girl of 5 years, developed two metastases in the upper lobe of the right lung 17 months after left nephrectomy. In response to actinomycin D one of these disappeared radiographically and the other decreased in size, then remained stationary. A second course of actinomycin D, 6 months later, produced no further change. Right upper lobectomy was performed on August 1, 1959. One metastasis was found to have been completely replaced by macrophages and appeared as a yellow plaque under the pleura and the other presented as a whitish nodule which microscopically showed a very attenuated picture of a secondary Wilms' tumour. This child has remained well up to the time of writing.

Were a similar case to be treated now, irradiation would be used after the first course of actinomycin D and, if inadequate, this would be followed by lobectomy.

The salvage rate in this group has thus proved considerable and the aggressive attitude to pulmonary dissemination seems to be justified. The treatment, however, is essentially a matter of combined therapy, using in their correct sequence chemotherapy, irradiation, and ablative surgery.

Lung metastases that show no response to chemotherapy or irradiation are probably unsuitable for surgery. Early massive lung secondaries are unlikely to respond to any therapy.

Other Metastases. Metastases in the liver are not suitable for irradiation, and we have had no success at all with actinomycin D. Bone metastases may show temporary regression with irradiation but recurrence seems to be the invariable rule. Actinomycin D was used in one case only and without effect.

Peritoneal recurrence has again been completely resistant to actinomycin D and has, in our hands, shown no noticeable response to irradiation. By the time these latter recurrences are manifest, of course, multiple organs tend to be involved.

Summary

A series of 18 successive cases of Wilms' tumour, treated by a régime of actinomycin D, nephrectomy, and irradiation, is recorded.

The recovery rate over a minimal two-year period was 62% as compared with 11.5% recorded in a previous series in which actinomycin D was not used.

The toxic effects of actinomycin D are discussed.

Treatment of pulmonary metastases is discussed in detail, and that of other metastases is mentioned.

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REFERENCES

- D'Angio, G. J., Farber, S., and Maddock, C. L. (1959). Potentiation of x-ray effects by actinomycin D. *Radiology*, 73, 175.
- Farber, S., D'Angio, G., Evans, A., and Mitus, A. (1960). Clinical studies of actinomycin D with special reference to Wilms' tumor in children. *Ann. N.Y. Acad. Sci.*, 89, 421.
- Howard, R. (1957). Nephroblastoma: Wilms' tumour. *Med. J. Aust.*, 1, 200.
- Philips, F. S., Schwartz, H. S., Sternberg, S. S., and Tan, C. T. C. (1960). The toxicity of actinomycin D. *Ann. N.Y. Acad. Sci.*, 89, 348.