MANAGEMENT OF WILMS' TUMOUR

By David Tan Boon Chee, M.B., B.S. and K. Paramathypathy, M.B., B.S., D.C.H.
(Paediatric Unit, Outram Road General Hospital, Singapore)

Wilms' Tumour (Nephroblastoma) is considered to be one of the treatable malignant tumours of infancy and childhood, if diagnosed carly. Various combinations and regimes of chemotherapy and radiotherapy have been devised in addition to surgery and as a result, cure rates have risen considerably. We have herein attempted to analyse the results in the treatment of 13 cases seen and treated in the Government Paediatric Units in Singapore between 1959 and 1969. As a comparison, an attempt has been made to summarise the results achieved and the regimes employed in other centres of the world to date. Finally, we have ventured to suggest a regime which could be usefully employed in Singapore with the cooperation of the Paediatricians, Surgeons and Radiotherapists in full consultation so that a better salvage rate could be obtained in this extremely malignant but nevertheless curable condition.

The records of the 13 cases of Wilms' Tumour diagnosed and treated between the years 1959 and 1969 show the following. (Table I).

COMMENTS

The sex ratio is M/F = 7/6. The average age of diagnosis was 2-3 years. Two cases are still living, both of which were less than 2 years of age at time of diagnosis. This conforms to the general observation that the prognosis is better if the primary tumour is diagnosed and treated before the patient is 2 years old. The patient who was diagnosed at 1 year of age is now about 5 years old (4-year survival) and is the only survivor out of seven who were treated with nephrectomy and radiotherapy. The other survivor is one of two who had the benefit of surgery, radiotherapy and Actinomycin-D and is alive 15 months postoperatively. The other who had similar treatment was diagnosed at 4 years of age but developed secondaries in the skull and liver after one year and died recently while on the priming part of a course of Vincristine.

Out of 13 cases, 3 each (i.e. 23%) died of metastases in the liver and lungs respectively. Other centres have reported a lower rate of secondaries to the liver, the lungs being the commonest site. Among those who died are included two who had widespread metastases and were not treated because the parents took them home and two others who had only radiotherapy because of metastases. In summary, of all those treated with nephrectomy and radiotherapy, only one (of 7) was above 2 years of age but his whereabouts are unknown. He has presumably died. Of the rest, only one has survived, i.e. 16.6% survival for this regime although diagnosed early. Only 2 of the series of 13 had the benefit of Actinomycin-D as well and one has survived to date. The other although diagnosed at 4 years of age had a one-year survival despite delay in surgical treatment. She was started on a regime of Vincristine (W.W. Sutow *et al*, 1963) and showed some regression of metastases in the skull and liver (Table II).

TABLE II

Period	Size of Metastases in Skull	Liver Size (Along Nipple Line)
Original size	4 cm.	7.0 cm.
After 7 days	3-5 cm.	6.5 cm.
After 12 days	2-5 cm.	6.5 cm.

HISTORICAL REVIEW

Klapproth (1959) reviewing the literature from 1940 to 1958 consisting of 1,127 treated cases found a survival of 20.9% following nephrectomy alone and 24.1% to 27.1% survival as a result of surgery and radiotherapy.

Actinomycin was isolated and crystallised in 1940 and introduced by S.A. Waksman as an antibiotic. However, Actinomycin-D was used for Wilms' Tumour only in 1954 (Farber, S. *et al*, 1960) and thereafter it has become the first recognised chemotherapeutic agent to be successfully used in Wilms' Tumour. It was also found to have a synergistic and potentiating effect on radiotherapy. It gained in prestige as a result of Howard's report of 18 consecutive cases seen and reported from the Royal Children's Hospital, Melbourne, in 1964. He reported an improvement from a 11.4% 2-year survival in 26 cases to more than 60% survival in 18 cases treated with surgery, radiotherapy and Actinomycin (Howard, R., 1964).

TABLE I

No. of Cases	Case No.	Sex	Age in Months	Chief Signs and Symptoms	I.V.P.	Treatment	Result (Survival in Months)	Remarks
2	1	F	24	Left abdominal mass Liver—enlarged	Not done	Nil (WIDESPREAD METASTASES)		Left hospital at parents' request
	2	M	12	Unable to pass urine one night Left abdominal mass Metastases in skull	Diagnostic			Left hospital at parents' request
2	3	M	36	Sudden abdominal pain Left abdominal mass Metastases in lungs	Not done	RADIOTHERAPY (WIDESPREAD METASTASES)		Presumed dead No follow-up
	4	M	54	Fever Left abdominal mass Lump in left side of neck	Not done			Presumed dead No follow-up
7	5	M	24	Haematuria Left abdominal mass	Unsatisfactory	NEPHRECTOMY AND RADIOTHERAPY	15/12	
	6	F	3	Abdominal distension since birth Right hypochrondrial distension	Diagnostic			Presumed dead No follow-up after 3/12
	7	M	15	Left abdominal mass Liver enlarged	Diagnostic		Living	
	8	M	24	Left abdominal mass	Non excreting	Tumour adherent to adjacent structures at laparotomy	8/12	Lung metastases at death
	9	M	26	Right abdominal mass	Non excreting		12/12	Lung metastases at death
	10	F	24	Right abdominal mass	Not done		8/12	
	11	F	60	Right abdominal mass	Not done	No evidence of invasion at laparotomy		Lost track of as probably gone back to Sibu Presumed dead
1	12	F	16	Pain and right abdominal mass Poor appetite	Diagnostic	NEPHRECTOMY ACTINOMYCIN-D RADIOTHERAPY	Living	Has had 2nd dose of Multiple dose therapy
1	13	F	48	Right abdominal mass	Atypical ? Neuroblastoma	NEPHRECTOMY ACTINOMYCIN-D RADIOTHERAPY } For Primary Tumour in 1968 VINCRISTINE — for secondaries which appeared in 1969	14/12	Bone and Liver metastases at death

Fernbach and Martyn (1966) in a masterly paper reported an overall survival of 70% out of 30 cases. 6 out of 14 treated with surgery and radiotherapy survived (i.e. 43%). 13 had in addition Actinomycin which was given in repeated doses to 10. 12 survived (i.e. 92%). He concluded that the drug is "cidal" to small but poorly established metastases as it is well known that Actinomycin does not permanently eradicate advanced metastatic disease. He was the first to try the multiple dose therapy.

Johnson, Maceira and Koop (1967) however, demonstrated that Actinomycin might lengthen survival without preventing recurrence.

Burcher and Ewen (1968) have also confirmed the efficacy of Actinomycin-D when the survival rate was more than doubled. They concluded among other things that a thoraco abdominal incision is essential (as advocated by Gross in 1948) to lessen the morbidity following surgery and that the presence of metastases need not mean a fatal result and that palliative excision should be considered. They also pointed out that early treatment and early introduction of Actinomycin-D makes the treatment of these tumours a surgical emergency.

In 1961-1962, the Paediatric Division of the Southwest Cancer Chemotherapy Study Group in the U.S. conducted an investigation on the efficacy of Vincristine, a new anti-tumour drug prepared from the periwinkle plant (Sutow *et al*, 1963). The responses were graded according to the following evaluation:—

Size of the lesion S = length × width.

Regression in size = 50% or more—definite response.

Regression in size = 20-50%—slight response.

Regression in size = 25%—no response.

There was definite response in 8 out of 13 cases. One showed a slight response. The response was apparent in 3 weeks in 75% of cases. However, the duration of the response was short, being 3-28 weeks (medium 8 weeks). There was no crossed resistance with Actinomycin-D and radiotherapy which was used in most of the cases prior to Vincristine. There were no serious myelosuppressive effects on the dosage used.

The same study group (Cancer Chemotherapy reports, 1968) tried Vincristine as an adjuvant preceding irradiation for metastatic disease. There was not much difference in the effect or the duration of response, when the drug was given alone, although the "possible cure" rate was slightly higher for combination therapy.

A comparative study of the usefulness of Vincristine and irradiation, Actinomycin-D and irradiation and a third group on Vincristine and Actinomycin-D and irradiation in metastatic disease is also being made but to date there has not been sufficient data.

In 1962, a pilot study was started at the University of Texas using Vincristine as an adjuvant in the primary treatment of Wilms' Tumour (Cancer Chemotherapy reports, 1968). This series reported in 1965 contains 8 survivals out of 9 patients, 7 of whom had a 2-year survival in 1968 (i.e. 79%) in spite of unfavourable factors in all children, namely over 2 years of age, invasion of vasculature, renal pelvis, capsule or adjacent structures and metastases to lymph nodes or bone marrow.

Sullivan in 1967 (Sullivan *et al*) reported on the efficacy of Vincristine Sulphate in place of pre-operative irradiation in two primary cases of Wilms' Tumour and two with inoperable secondaries in the lungs. Results have been encouraging, there having been no recurrence over periods between 21 months and 5 months.

A study of the efficacy of the 2 chemotherapeutic agents, Actinomycin-D and Vincristine, as adjuvants in primary therapy for Wilm's Tumour has been started by the Paediatric Division of the Southwest Cancer Chemotherapy Study Group. As Vincristine is comparatively free of myelo-suppressive effects in the dosages used and in the absence of cross resistance with Actinomycin-D and irradiation and as the toxicities of Vincristine and Actinomycin-D are dissimilar, the drug effects should be additive. With the combination therapy, the cure rate should approach 100%.

The Children's Cancer Study Group A reporting from the Columbia-Presbyterian Medical Centre began a controlled cooperative study in November 1964 and compared the results of a single dose Actinomycin therapy as an adjunct to surgery and radiotherapy and a multiple maintenance dose therapy (Wolff *et al*, 1968). They demonstrated that in children over 12 months of age and with resectable forms of Wilms' Tumour, 19 of 22 (86%) on the multiple course therapy and 11 of 23 (48%) on the single course therapy, had no recurrences although all of them had not been followed up more than 18 months.

CHEMOTHERAPEUTIC AGENTS

Actinomycin-D, Dactinomycin or "Cosmogen" (Merck, Sharpe and Dohme)

This drug was developed from Actinomyces (Streptomyces) antibioticcus. There appears to be some evidence that it acts complimentary to irradiation in that the former inhibits ribose-neucleic acid (R.N.A.) and protein synthesis while irradiation inhibits only deoxyribose nucleic acid (D.N.A.) synthesis. It is believed resistance to the drug does develop.

It is available in the form of an amorphous yellow powder in 0.5 mg. ampoules. It is given intravenously and is made into a clear gold coloured solution with distilled water. This has to be used at once. It is a very toxic drug and extravenous injection causes a severe local reaction. Leucopenia and thrombocytopenia are the other toxic effects. Anorexia, nausea, stomatitis, diarrhoea and stunting have been reported as some of the side efforts.

Vincristine Sulphate or "Oncovin" (Lilly)

This is an alkaloid derived from the ever-blooming ornamental subshrub periwinkle (Catharanthus roseus G. Don) (Vinca rosea Linn) and is available as a powder in 1 gm. or 5 mg. ampoules which can be made up into a solution for intravenous therapy using the accompanying diluting solution of 10 c.c. containing sodium chloride 0.9% benzyl alcohol as a preservative. The made-up solution is potent for 14 days if kept in a refrigerator. The mechanism of inhibition of tumour growth is unknown. It is supposed to produce a typical C-mitotic effect. It does not interfere with R.N.A. or D.N.A. synthesis but is believed to interfere in the metabolic pathway from glutamic acid to the citric acid cycle and urea. It is administered intravenously at weekly intervals. Extravasation should be avoided as considerable irritation is caused.

It was first administered to a human on June 1st, 1961, for lymphoblastoma which showed some shrinkage. The most common side effect is alopecia. Others are vomiting, nausea, abdominal pain, pain in the jaw, nervousness, ataxia, fits, haematuria and rarely leucopenia. Neuromuscular disturbances are more troublesome than bone marrow toxicity. The side effects are reversible and related to dosage.

DISCUSSION

A few salient points can be gathered from the results in our cases and a study of the work and results in other centres.

Case 2 demonstrates the fact that metastases can occur at even one year of age.

The prognosis is better in the cases which are diagnosed within the first 2 years of life probably because there is a shorter period of time during which the tumour could have gone unnoticed. A combination of surgery, radiotherapy and Actinomycin-D has shown a remarkable improvement in the cure rates. The "Cidal" effect of Actinomycin-D on small but poorly established metastases might mean that survival is prolonged by the prevention of new metastases from unnoticed established lesions till the latter are removed surgically later. The improved results using the multiple dose therapy go to prove this. A corollary would be that these patients might need to be followed up for longer periods before being pronounced cured. The advent of Vincristine which has no cross resistance with Actinomycin-D is a decided boon as preliminary reports show that Vincristine by itself gives good results in primary Wilms' Tumour. Although it is less useful in cases with secondaries, it certainly helps to make inoperable cases operable and thereby enhances the chances of a cure. There is no place for preoperative radiation except perhaps in conjunction with Vincristine in inoperable cases.

Our figures are without doubt unsatisfactory, although differences in results can be caused by variation in case material. Improvement could be achieved by greater awareness of the condition, early diagnosis and urgency in concerted management having appreciated the cure rates that can be attained. There needs to be more coordination and consultation between Paediatrician who should be generally responsible and Surgeon and Radiotherapist. A definite method of treatment should be agreed upon. It is hoped that the following protocol would be useful. The dosages of the drugs may have to be modified as we gain more experience, as they are used for the local population. It is suggested that, in future, cases be treated under two main categories because of the present prohibitive cost of Vincristine:—

(A) Without Vincristine

(B) With Vincristine

The Paediatrician should be notified as soon as a case of Wilms' Tumour is diagnosed. He will then examine the patient and decide under which category he would be placed, usually depending on the availability of Vincristine. The Surgeon and Radiotherapist will then be consulted before mapping out the details of treat-

ment. A total follow-up for 5 years is recommended although 2-year survival as a cure is now universally accepted. Patients should be seen every 2 weeks for 1 year for haematological check-up and every 4 weeks for chest X-rays. Urine should be examined at intervals. Thereafter check-up should be monthly for 1 year and 3 monthly for the next 3 years.

(A) **Without Vincristine**

(1) Primary tumour with no evidence of secondaries.

Initial therapy with Actinomycin-D.

(a) Actinomycin-D. Total dose = 120 microgram/kg. in 8 equal intravenous injections.

(b) Administered on days 1, 2, 3, 4, 5, 7, 9 and 12 (A daily monitoring of the total white count, platelet count and the haemoglobin level should be made).

(c) Nephrectomy on 3rd day. Detailed surgical notes regarding extent of tumour necessary.

(d) Commence irradiation on 26th day and to continue daily to total dose of 3,000 rads over approximately 28 days. The total white count, platelet count and haemoglobin should be checked daily before irradiation.

Maintenance therapy with Actinomycin-D.

(a) Each course consisting of a total dose of 75 microgram/kg. in 5 equal doses on 5 successive days. The blood count should be monitored daily and treatment withheld if the platelet count drops below 150,000/c. cm.

(b) The above dose should be given at 6 weeks, 3 months, and every 3 months until 15 months after operation.

(2) Primary tumour inoperable or with secondaries—Vincristine should be used as seen below.

(B) **With Vincristine**

(1) Primary tumour with no evidence of secondaries.

(a) Nephrectomy on diagnosis.

(b) Vincristine .05 mg./kg./day intravenously weekly for 8 weeks.

(c) Actinomycin-D 15 microgram/kg. intravenously daily for 5 days, monthly for 2 courses.

(d) Irradiation of renal bed daily for a total dose of 1,200-2,000 rads.

(e) Maintenance therapy with Actinomycin-D at 3 monthly intervals until 15 months after operation, using a total dose of 75 microgram/kg. intravenously for 5 days.

(2) Primary tumour inoperable at diagnosis.

(a) Preoperative—Vincristine 0.05 mg./kg. each dose for 2-4 doses at intervals of 5-8 days between doses.

(b) Nephrectomy.

(c) Irradiation of renal bed.

(d) Vincristine 0.05 mg./kg. intravenously each week for 12 doses.

(e) Actinomycin-D 15 microgram/kg. intravenously daily for 5 days, 3 months later and at 3 monthly intervals for 15 months after operation.

(3) Metastatic Disease.

(a) Vincristine—priming dose of 0.02 mg./kg./daily for 5 days.

(b) Maintenance dose of 0.05 mg./kg./weekly for 12 doses.

(c) Surgical, e.g. lobectomy, hemihepatectomy, etc. as indicated.

SUMMARY

An analysis is made of the management and results of 13 cases of Wilms' Tumour over a period of 10 years. A brief summary of methods and results obtained in other centres has been made in an attempt to draw up a protocol so that uniformity may be obtained in the treatment of local cases of Wilms' Tumour in Singapore. In this manner, we hope that experiences may be shared so that:—

1. Variation in dosage may be made to suit local children.
2. Minor alteration regarding mode of administration may be made.
3. Combined local figures for this Hospital, and for that matter for Singapore, may be produced in future with the hope that the cure rate may be nearer the ideal 100%.

ACKNOWLEDGEMENT

We wish to thank all the Paediatricians, Surgeons and Radiotherapists and staff who have in the past cared for the cases referred to.

REFERENCES

1. Burcher, S. K. and Ewen, K. M. (1968): "Nephroblastoma—Wilms' Tumour". New Zealand, Med. J., 68, 89.
2. Farber, S. (1966): "Chemotherapy in Treatment of Leukaemia and Wilms' Tumour." J. Amer. Med. Ass., 198, 826.
3. Farber, E. *et al* (1960): "Clinical Studies of Actinomycin-D with special reference to Wilms' Tumour in Children." Ann. N.Y. Acad. Sci., 89, 421.
4. Fernbach, D. J. and Martyn, D. T. (1966): "Role of Dactinomycin in the improved survival of children with Wilms' Tumour." J. Amer. Med. Ass., 195, 1005.
5. Howard, R. (1964): "Nephroblastoma (Wilms' Tumour): improved prognosis with Actinomycin-D." Med. J. Aust., 2, 141.
6. Johnson, D. G., Maceira, F., Koop, C. E. (1967): "Wilms' Tumour treated with Actinomycin-D; the relationship of age and extent of disease to survival." J. Paed. Surg., 2, 13.
7. Sullivan, M. P. (1968): "Vincristine (N.S.C.-67574) Therapy for Wilms' Tumour." Cancer Chemotherapy Reports, 52, 481.
8. Sullivan, M. P., Wataru, D., Sutow, D., Cangir, A., Taylor, G. (1967): "Vincristine Sulphate in Management of Wilms' Tumour." J. Amer. Med. Ass., 202, 381.
9. Sutow, W. W., Thurman, W. G., Windmiller, J. (1963): "Vincristine (Leucocristine) Sulphate in the treatment of metastatic Wilms' Tumour." Pediatrics, 32, 880.
10. Wolff, J. A., Krivit, W., Newton, Jr., W. A., D'Angio, G. J. (1968): "Single versus multiple dose Dactinomycin therapy of Wilms' Tumour." New Eng. J. Med., 279, 290.