2. Shaikh NA, Owen AM, Gilchik MW, *et al.* Actions of medroxyprogesterone acetate on the efficacy of cytotoxic drugs: studies with human breast cancer cells in culture. *Int J Cancer* 1989, **43**, 458–463.
3. Gilchik MW, Shaikh NA, Beranek PA, *et al.* Cyclical sequential hormonochemotherapy in the treatment of advanced breast cancer. *Br Med J* 1987, **295**, 1172.
4. Shaikh NA, Owen AM, Gilchik MW, *et al.* Adriamycin action on human breast cancer cells: enhancement by medroxyprogesterone acetate. *Int J Cancer* 1989, **43**, 733–736.
5. Gundersen S, Kvinnsland S, Klepp O, *et al.* Chemotherapy with or without high-dose medroxyprogesterone acetate in estrogenreceptor negative advanced breast cancer. A randomized study. *Eur J Cancer* 1992, **28A**, 390–394.
6. Hayward JL, Carbone PP, Heuson, *et al.* Assessment of response to therapy in advanced breast cancer. *Cancer* 1977, **39**, 1289.
7. Peto R, Pike MC, Armitage, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.
8. Gundersen S, Kvinnsland S, Klepp O, *et al.* Weekly anthracycline in the treatment of advanced breast cancer. *Acta Oncol* 1989, **28**, 883–885.

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Adult Wilms' Tumour: Review of 22 Cases

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The Institut Gustave Roussy experience with nephroblastoma in 22 patients older than 16 years during a 19-year period (1973–1992) was retrospectively reviewed. All patients underwent a nephrectomy. There were 4 stage I, 8 stage II, 3 stage III and 7 stage IV patients. Initial postnephrectomy therapy included single modality approach in 7 patients (radiotherapy in 1 and chemotherapy in 6) and combined modality approach (radiotherapy and chemotherapy) in 15 patients. The agents used most often were actinomycin, vincristine and doxorubicin. 2 of 7 (29%) and 7/15 (47%) patients are disease-free survivors after first-line treatment. Salvage chemotherapy was given in 13 patients. Only 1 patient experienced a subsequent sustained complete remission. After a mean follow-up of 100 months (range 10–240), 12/22 patients (55%) are alive, including 10 who are disease-free (45%). We confirm that adult patients are likely to have more advanced disease and poorer prognosis than children. The combined modality approach is more active than one-modality therapy. Aggressive treatment, including the three-drug regimen actinomycin + vincristine + doxorubicin, regardless of stage, associated to irradiation starting from stage II, is recommended.

Key words: adult, nephroblastoma, Wilms' tumour, treatment
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INTRODUCTION

NEPHROBLASTOMA IS a disease of young children accounting for approximately 5–10% of all paediatric neoplasms. Although the occurrence of nephroblastoma in adults is infrequent, the exact incidence remains undetermined, since reports of adult patients before 1960 are difficult to interpret, and histopathological criteria for the diagnosis are not well defined [1, 2]. Thus, 80% of 192 cases gathered from the literature by Kilton and colleagues in 1980 were excluded because of lack of or unconvincing photomicrographs or incomplete histological descriptions [3]. However, Jagazia and colleagues found a 9.2% incidence of adults among patients with nephroblastoma seen at one institution during a 14-year period [4]. The incidence was estimated as 3% by Slevin and colleagues [5].

Compared to their paediatric counterparts, adult patients are assumed to have more advanced disease, relapse more frequently and respond poorly to therapy [6]. However, since 1979, a notable improvement in response and survival has been noted in adult patients when modern multimodal therapy is employed [7]. To better define the outlook of this disease in adults, we have reviewed our experience with patients older than 16 years of age with nephroblastoma treated in our institution between 1973 and 1992.

PATIENTS AND METHODS

Between 1973 and 1992, 22 patients ≥ 16 years old were referred to our institution for renal cell tumour defined histologically as nephroblastoma. Patients' characteristics, stage of disease, treatment and outcome were analysed according to a retrospective review of case files. All pathological specimens were reviewed at our institution and classified as either favour-

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able or unfavourable histology. Extension of the disease was determined by abdominal scan and/or abdominal sonography, chest X-ray and chest scan. Staging of the disease was established at surgery according to the SIOP (Société Internationale d'Oncologie Pédiatrique) staging system: stage I, when the tumour is confined to the kidney and is totally excised; stage II, when the tumour extends beyond the kidney but is totally excised; stage III, if there is residual tumour below the diaphragm or if there has been massive tumour spillage; stage IV, when distant metastases are present; and stage V, in case of bilateral renal involvement at diagnosis [8].

Treatment strategy was mostly derived from currently available paediatric regimens according to SIOP protocols. Response to therapy was evaluated according to the WHO criteria [9]. Response duration was measured from the time of response until the onset of progressive disease. Disease-free survival (DFS) was calculated from the time of macroscopic disappearance of the disease until disease relapse. Survival was calculated from the time of initial diagnosis to death or last follow-up visit.

RESULTS

22 adult patients were referred and treated at our institution during a 19-year period. Patients were numbered according to the year of diagnosis and their characteristics are summarised in Table 1. Patients ranged in age from 16 to 40 years with a median of 24 years. There were 14 females and 8 males. The renal tumour was located on the right side in 14 cases and on the left in 8 cases. Follow-up ranged from 10 to 240 months with a median of 100 months. The presenting signs were pain (18 cases), heamaturia (6 cases) and abdominal mass (4 cases). 2 patients experienced fever and 1 patient suffered from arterial hypertension. Clinical signs were completely absent in 1 patient in whom the disease was accidentally diagnosed during a gynaecological sonographic examination. All patients except 1 underwent nephrectomy in other hospitals. Histological review revealed nephroblastoma with favourable histology (FH) in 21 patients and unfavourable histology (UH) in 1 other (case 21). There were 4 patients with stage I, 8 patients with stage II, 3 patients with stage III, 7 patients with stage IV and none with stage V disease. 2 patients (cases 7 and 8) were classified as stage III because of tumour spillage during surgery. Postoperative chemotherapy and irradiation to the tumour bed or to metastatic sites were derived from available paediatric treatment strategies according to histology and stage of disease. One patient who was elsewhere received post-operative irradiation only, 6 patients received chemotherapy alone and 15 patients were treated with combined modalities.

Table 2 summarises the treatment and outcome of the 7 patients treated with one-modality therapy. Patient 6 was the only patient of our series who did not receive postoperative chemotherapy because of patient refusal. She received radiotherapy to the renal fossa for a stage II node-negative disease and relapsed 5 years later in the lung. Chemotherapy for 6 patients included a two-drug regimen with actinomycin (Ac) and vincristine (V) for 2–6 months in 4 patients VAc + epirubicin (Epi) for 6 months in 1 patient, and alternating V + doxorubicin (AD) with VAc and VP16 + carboplatin in 1 patient. Only 2 patients are still disease-free. These 2 patients (cases 14 and 19) were stage I and received 4 and 6 months of VAc. 2 patients relapsed: 1 stage II patient relapsed 20 months after initial complete response (CR) in the lung (patient 20) and 1 stage I patient relapsed in the liver after a 4-year disease-free interval (patient 10). 2 other patients progressed while on chemotherapy: patient 21 who had a stage IV UH, and patient 13 who progressed in the lung after 2 months of VAc.

Table 3 summarises the treatment and outcome of the 15 patients who received an initial multimodality therapy. Chemotherapy consisted of Ac alone for 3 patients (cases 1–3), VAc for

Table 1. Patients' characteristics and outcome

Patient no.	Date*	Age (years)	Sex	Histology	SIOP stage	Site of distant metastases	Outcome after initial therapy	Current status	Survival (months)
1	1973	22	F	FH	III		PD	DOD	6
2	1974	17	F	FH	IV	Lung	PD	DOD	7
3	1977	16	F	FH	II		PD	DOD	64
4	1977	17	M	FH	II		NED	NED	240+
5	1979	18	F	FH	II		Relapse	NED	168+
6	1980	25	F	FH	II		Relapse	AWD	156+
7	1983	25	M	FH	III		NED	NED	120+
8	1983	23	F	FH	III		Relapse	DOD	25
9	1983	16	F	FH	IV	Lung	CR	NED	120+
10	1983	19	M	FH	I		Relapse	DOD	84
11	1984	25	M	FH	II		NED	NED	108+
12	1986	16	F	FH	IV	Liver, lung	PD	DOD	64
13	1986	22	F	FH	I		PD	DOD	29
14	1987	28	F	FH	I		NED	NED	72+
15	1988	40	M	FH	IV	Lung, bone	PD	DOD	25
16	1988	26	M	FH	II		PD	DOD	12
17	1989	39	M	FH	II		NED	NED	48+
18	1990	37	F	FH	IV	Lung, peritoneum	CR	NED	36+
19	1991	17	F	FH	I		NED	NED	23+
20	1992	19	M	FH	II		Relapse	AWD	23+
21	1992	26	F	UH	IV	Lung	PD	DOD	12
22	1992	18	F	FH	IV	Lung	CR	NED	10+

*Date of initial diagosis. FH, favourable histology, UH, unfavourable histology; SIOP, Société Internationale d'Oncologie Pédiatrique; PD, progressive disease. NED, no evidence of disease; CR, complete remission; PR, partial remission; DOD, dead of disease; AWD, alive with disease.

Table 2. Outcome after one-modality therapy (7 patients)

Patient no.	Initial stage	Modality/regimen	Chemotherapy duration (months)	Outcome	DFS (months)	Site of relapse/ progression
6	II	RT tumour bed	—	Relapse	60	Lung
10	I	VAc	6	Relapse	48	Liver
13	I	VAc	2	PD	—	Lung
14	I	VAc	6	NED	72+	—
19	I	VAc	4	NED	23+	—
20	II	VAc + Epi	6	Relapse	20	Lung
21	IV	VAc/VAD; VP16 + CBCDA	3	PD	—	Lung, liver

RT, radiotherapy; PD, progressive disease; NED, no evidence of disease; DFS, disease-free survival; V, vincristine; Ac, actinomycin; Epi, epirubicin; CBCDA, carboplatin.

Table 3. Outcome after multimodality therapy (15 patients)

Patient no.	Initial stage	Treatment	Chemotherapy duration (months)	Outcome	DFS (months)	Site of progression/relapse
1	III	RT abdomen Ac	3	PD	—	Bone
2	IV	RT lung Ac	2	PD	—	Lung
3	II	RT tumour bed Ac	3	PD	—	Lung
4	II	RT Tumour bed + med. VAc	12	NED	240+	—
5	II	RT Tumour bed VAc	2	Relapse	6	Lung
7	III	RT Abdomen VAc + AD	6	NED	120+	—
8	III	RT Abdomen VAc + AD	12	Relapse	16	Peritoneum, lung
9	IV	RT abdomen + chest VAc + AD	6	NED	120+	—
11	II	RT tumour bed VAc + AD	9	NED	108+	—
12	IV	RT chest + liver VAc + AD	3	PD	—	Lung
15	IV	RT tumour bed + bone VAc + Epi	2	PD	—	Lung
16	II	RT tumour bed AD + Velbe + Ac + C	3	PD	—	Lung, liver, peritoneum
17	II	RT abdomen VAc + Epi	3	NED	48+	—
18	IV	RT abdomen Liver surgery VAc + Epi	6	NED	36+	—
22	IV	RT tumour bed + RLN + chest VAc + Epi/ V + Epi + VP16	—	CR	10+	—

RT, radiotherapy; V, vincristine; Velbe, vinblastine; Ac, actinomycin; AD, doxorubicin; Epi, epirubicin; C, cyclophosphamide; RLN, retroperitoneal lymph nodes; Med, mediastinum; PD, progressive disease; NED, no evidence of disease; CR, complete remission; DFS, disease-free survival.

2 patients (cases 4, 5), and a three-drug combination including VAc and an anthracyclin (AD or Epi) in 8 others. Patient 16 received a four-drug combination without vincristine, and patient 22, an alternation of VAc + Epi and V + Epi + VP16. Radiotherapy to the tumour bed and/or to the abdomen *in toto* was delivered to 13 patients. 2 of them received an additional chest irradiation for lung metastatic disease (patients 9 and 22). 2 other patients received radiotherapy to the chest alone (patient 2) or to the liver and chest (patient 12). It is of note that patient 18 had had initial surgical resection of metastases from the liver and the peritoneum before whole abdominal irradiation and chemotherapy. 7 of 15 patients are still disease-free, including 3 stage II patients (cases 4, 11, 17), 1 stage III (patient 7) and 3 stage IV (patients 9, 18, 22). 2 patients with initial stage II and

III relapsed after 6 and 16 months of DFS in the lung and the lung and peritoneum, respectively (patients 5 and 8). 6 patients progressed while on chemotherapy (patients 1–3, 12, 15, 16), including the 3 patients who received monochemotherapy with Ac.

Salvage therapy was undertaken in 13 patients, 5 of them after initial one-modality therapy and 8 after multimodality therapy (Table 4). 8 patients had progressive disease and 5 had relapsed after initial CR. Median DFS was 26 months (range 5–60). 7 patients experienced an objective response including 6 CR and 1 partial response (PR). However, only 1 patient (patient 5) is still without evidence of disease after 2 courses of VAD followed by complete surgical resection of residual lung metastases and a whole chest irradiation at 12 Gy. The other 6 responders relapsed after a median response duration of 9 months (range 4–18 months). It is of interest to note that all the responders were at initial stage I or II and that 4/6 CRs had initially responded and subsequently relapsed before retrieval therapy. As shown in Table 4, the salvage chemotherapy was variable and was associated with irradiation or surgery in 4 patients. Thus, the individual contribution of each drug could not be determined. However, the addition of doxorubicin to VAc produced a CR in patients 3, 5, 10 and 13 after initial failure with VAc.

Currently, 12 patients (55%) are alive, 10 of whom are disease-free. 2 patients are alive with disease after the fifth (patient 6) or second (patient 20) line of treatment. When we consider the initial patient stage, 8 are alive (67%) and 4 died from progressive disease (PD) among the 12 patients with stage I or II. 4 patients are alive (40%) and 6 died from PD among the 10 stage III or IV patients. 2 of 7 (29%) patients treated with the one-modality approach are disease-free survivors as compared to 7/15 (47%) patients who received a combined modality approach as first-line treatment.

DISCUSSION

There has been steady improvement in the management of childhood nephroblastoma in the last two decades. The 5-year survival of 509 children treated by the SIOP-6 trial was 89% [10]. The most powerful markers of adverse prognosis are the presence of UH and tumour stage [11]. The prognostic value of histology was not evidenced in our adult series since only 10 of 21 patients with FH are currently disease-free.

It has been assumed that adults with Wilm's tumour have a poorer prognosis than children. This impression was drawn from multiple case reports [1, 2, 4, 5, 12] describing a total of 18 adult patients who died from progression of their disease despite multimodal therapies. This poor outcome of nephroblastoma in adults was rendered more convincing when Byrd and colleagues [6] reviewed the fate of 31 adult patients reported to the National Wilms' Tumour Study-1 (NWTS-1). Authors found that the prognosis was worse than in children stage-for-stage, with an overall 3-year actuarial survival rate of 24%.

Our study included 22 adult patients referred to our institution during an 18-year period. There were 7 patients with metastatic disease (32%) which is comparable to the 40% and 29% rates found by Arrigo and colleagues [7] and Byrd and colleagues, respectively [6]. These proportions of adult patients with metastatic disease are greater than that found in children (10% in NWTS-1 and 12% in SIOP-6) [10, 11]. In fact, the true proportion of patients with metastases in our study could be higher since a chest scan was rarely done (6 patients), thus underestimating the stage of the disease. The 55% overall survival rate of our patients, after a mean follow-up period of 100 months compares unfavourably with those currently being achieved in children. The 3-year survival of children with FH disease was 91% in NWTS-2 and -3 [11]. However, our results are very close to the recent report of Arrigo and associates

Table 4. Response to salvage (second-line) therapy (13 patients)

Patient no.	Initial stage	Status before treatment	Time to relapse (months)	Treatment (duration in months)	Response	Duration of response (months)
1	III	PD	—	RT bone	PD	—
2	IV	PD	—	VAc + AD (2)	PD	—
3	II	PD	—	VAc/VAD (8)	CR	18
5	II	Relapse	10	VAD (2) Lung: RT + surgery	CR	144+
6	II	Relapse	60	VAc/VAD (6)	CR	12
8	III	Relapse	16	Vd + Ac + DTIC + CDDP (4)	PD	—
10	I	Relapse	48	Liver surgery VAD (4)	CR	4
12	IV	PD	—	VP16 (2)	PD	—
13	I	PD	—	VAc + AD (4)	CR	6
15	IV	PD	—	IVA (4)	PD	—
16	II	PD	—	VP16 + CDDP (3) Liver surgery RT abdomen	PR	9
20	II	Relapse	20	VP16 + CBCDA (6) Lung: RT + surgery	CR	4
21	IV	PD	—	VP16 + CBCDA (3)	PD	—

PD, progressive disease; RT, radiotherapy; V, vincristine; Ac, actinomycin; AD, doxorubicin; Vd, vindesine; IVA, ifosfamide + V + Ac; CDDP, cisplatin; CBCDA, carboplatin; CR, complete response; PR, partial response.

dealing with adult patients treated between 1979 and 1987, where the 3-year survival rate was 67% [7]. This better survival compared to the series of Byrd and colleagues [6] may have been due to the introduction of combined modality treatment as applied to children. The subdivision of our patients into two groups, according to the modality of initial treatment, gives some evidence that multimodality therapy led to a true higher cure rate. There were only two disease-free survivors (29%), among 7 patients treated with one modality, and five failures, including 2 patients with stage I disease. In contrast, 7 disease-free survivors of 15 patients (47%) were obtained by the combined modality treatment, including 1 stage III and 3 stage IV patients. Other sustained complete remissions in adult patients have been reported using this combined modality approach [3, 13–17].

Five of the 10 deaths in our study occurred more than 2 years after diagnosis, which means that further relapses in adults continue after 2 years. Similarly, Byrd and associates found that 13 of 20 deaths of their adult series occurred from 2 to 4 years after diagnosis. In contrast, death occurs mostly in the first 2 years in children [10, 11]. The retrieval therapy was disappointing, resulting in only 1 NED among 13 treated patients. This surviving patient (patient 5), originally stage II, was salvaged by two courses of VAD, followed by complete surgical resection of residual lung metastases and a whole chest irradiation. This patient had refused further chemotherapy, therefore, suggesting that surgery and/or radiotherapy to individual metastases may occasionally be of curative value. The response rate to salvage therapy in children is low with only 17 survivors of 71 relapsed children according to Pinkerton and colleagues [18] and a 30% 3-year postrelapse survival according to Grundy and associates [19]. Pharmaceuticals known to be effective in salvage therapy, such as VP16, cisplatin, carboplatin or ifosfamide [15, 18], were used in 7 relapsed patients. Short objective responses were obtained in 2 patients (patients 16 and 20), who received VP16 and a platinum derivative. The only useful fact from our experience in salvage therapy is that the addition of doxorubicin to VAc offered an unequivocal benefit in term of response and survival. This fact confirms that this three-drug combination is the most curative regimen of the disease. The role of high-dose chemotherapy with bone marrow or peripheral blood stem cell rescue remains to be determined in the salvage setting [16].

We conclude from our data that guidelines for treatment strategy in adult patients should involve aggressive treatment rather than refinement or reduction, as is the case in children [10], or as concluded by Arrigo and colleagues in their adult series [7]. We believe that the three-drug regimen with actinomycin, vincristine and an anthracyclin must be uniformly prescribed to all patients regardless of stage, since 2/4 stage I patients failed the two-drug regimen without doxorubicin (patients 10 and 13), and since the cure rate in salvaged patients is dismal whatever the initial stage. However, chemotherapy duration could be adapted for stage: 6 months for stage I and at least 12 months starting from stage II. Radiotherapy for stage I patients is not recommended. The irradiation of the tumour bed in stage II patients seems wise, since the potential of damage to growing bone after irradiation is not an issue in adults. However, none of our 8 stage II patients relapsed in the tumour bed. Patients with stage III or IV must also benefit from irradiation to the abdomen and to all the other metastatic sites.

1. Esersky G, Saffer S, Panoff C, Jacobi M. Wilms' tumor in the adult: review of literature and report of three additional cases. *J Urol* 1947, **58**, 397–411.
2. Smith K. Wilms' tumor in the adult. *Br J Surg* 1960, **47**, 397–400.
3. Kilton L, Matthews M, Cohen M. Adult Wilm's tumor: a report of prolonged survival and review of the literature. *J Urol* 1980, **124**, 1–5.
4. Jagasia K, Thurman W. Wilms' tumor in the adult. *Arch Intern Med* 1965, **155**, 322–325.
5. Slevin N, McWilliam L, Pearson D. Adult nephroblastoma. Five cases treated by surgery, radiotherapy and chemotherapy. *Clin Radiol* 1987, **38**, 483–486.
6. Byrd R, Evans E, D'Angio G. Adult Wilms' tumor: effect of combined therapy on survival. *J Urol* 1982, **127**, 684–651.
7. Arrigo S, Beckwith J, Sharples K, D'Angio G, Haase G. Better survival after combined modality care for adults with Wilms' tumor. A report from the National Wilms' Tumor Study. *Cancer* 1990, **66**, 827–830.
8. Lemerle J, Voute P, Tournade MF, *et al.* Pre-operative versus post-operative radiotherapy single versus multiple courses of Actinomycin D in the treatment of Wilms' tumor. *Cancer* 1976, **38**, 647–654.
9. World Health Organization. *WHO Handbook of Reporting the Results of Cancer Treatment.* WHO offset publication no. 48, WHO, Genova, 1979.
10. Tournade MF, Com-Nouge C, Voute P, *et al.* Results of the Sixth International Society of Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor. *J Clin Oncol* 1993, **11**, 1014–1023.
11. The National Wilms' Tumor Study Committee. Wilms' tumor: status report, 1990. *J Clin Oncol* 1991, **9**, 877–887.
12. Bard R, Greenwald E, Kalnicki S, Sablay L. Adult Wilms' tumor treated with radiotherapy and chemotherapy: a case report. *J Urol* 1979, **121**, 679–680.
13. Obsen B, Bischoff A. Wilms' tumor in an adult. *Cancer* 1970, **25**, 21–25.
14. Abratt R, Preez M, Kaschula R. Adult Wilms' tumor. Cisplatin and etoposide for relapse after adjuvant chemotherapy. *Cancer* 1990, **65**, 890–892.
15. Dawson N, Klein M, Taylor G. Salvage therapy in metastatic adult Wilms' tumor. *Cancer* 1988, **62**, 1017–1021.
16. Hupperets P, Havenith M, Blyham G. Recurrent adult nephroblastoma. Long-term remission after surgery plus adjuvant high-dose chemotherapy, radiation therapy and allogenic bone marrow transplantation. *Cancer* 1992, **69**, 2990–2992.
17. Boyer C, Brickner T, Perry R. Cure of adult Wilms' tumor with distant metastasis? A case report. *AJR* 1968, **103**, 823–826.
18. Pinkerton C, Groot-Loonen J, Morris-Jones P, Pitchard J. Response rates in relapsed Wilms' tumor. *Cancer* 1991, **67**, 567–571.
19. Grundy P, Breslow N, Green D, Sharples K, Evans A, D'Angio G. Prognostic factors for children with recurrent Wilms' tumor. Results from the second and third National Wilms' Tumor Study. *J Clin Oncol* 1989, **7**, 638–647.

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