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Adjuvant chemotherapy with vinblastine, Adriamycin, and UFT for renal-cell carcinoma

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Summary. VAU therapy (vinblastine, Adriamycin, and UFT) was given postoperatively to 31 patients with stage I, II, or III renal-cell carcinoma, and the incidence of relapse as well as the survival of patients were studied. Administration was started at 7–14 days post-surgery; 5 mg/m^2 vinblastine and 30 mg/m^2 Adriamycin were given i.v. once every 4 weeks for a total of five courses, and three capsules of UFT (containing 300 mg tegafur) were given p.o. every day for 2–3 years. The postoperative observation period ranged from 2 years and 6 months to 7 years and 1 month (mean, 4 years and 2 months). The 1-year survival of patients was 100%, and the 3- and 5-year survival values were 96%. These results were significantly better (P <0.01) than the respective values (81%, 72%, and 60%) obtained for the historical controls, i.e., the 60 patients with stage I, II, or III renal-cell carcinoma who received no chemotherapy. Side effects such as alopecia, gastrointestinal symptoms, and myelosuppression were encountered, but all symptoms were so mild and transient that discontinuation of the treatment was not necessary. As VAU therapy might be useful as adjuvant chemotherapy for renal-cell carcinoma, it seems to merit further study.

Introduction

Postoperative combination chemotherapy has been used in attempts to improve the prognosis for patients with renal-cell carcinoma. However, no especially effective anticancer agent for renal-cell carcinoma has been found, and there has been no report of distinct improvement in the survival of patients due to the use of combined postoperative adjuvant chemotherapy.

In the present study we used combined therapy with three agents, including vinblastine and Adriamycin, which are believed to be relatively effective against renal-cell carcinoma, and UFT, which has produced good results in our previous experience, as postoperative chemotherapy (VAU regimen) for renal-cell carcinoma. The results are reported in this paper.

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Patients and methods

We used VAU therapy in 31 patients (22 men and 9 women) with stage I, II, or III renal-cell carcinoma in whom the tumor was considered to have been completely resected surgically during the 5-year period between 1984 and 1988. The age of our subjects ranged from 39 to 68 years (mean, 58 years). The right kidney was affected in 16 patients and the left kidney was affected in 15. The histological atypia of renal-cell carcinoma was rated as grade 1 to grade 3, and the stage was classified according to the system described by Robson et al. [6]. Histological grading yielded 14 grade 1 tumors and 17 grade 2 tumors; none of the tumors was classified as grade 3. In all, 15 patients had stage I disease, 10 had stage II disease, 4 had stage III A disease, and 2 had stage III B disease (Table 1).

The anticancer agents comprising the VAU regimen incluced vinblastine (VLB), Adriamycin (ADM), and UFT. Administration was started at 7–14 days postsurgery; 5 mg/m^2 VLB and 30 mg/m^2 ADM were given i.v. once every 4 weeks for a total of five courses, and three capsules of UFT (containing 300 mg tegafur) were given orally every day for 2–3 years (Table 2). All 31 patients were evaluated for postoperative relapse, survival, and toxicity. The postoperative observation period ranged from 2 years and 6 months to 7 years and 1 month (mean, 4 years and 2 months).

A total of 60 patients (45 men and 15 women) who had been examined during the period between 1974 and 1983 and who had received no chemotherapy served as historical controls. Their age ranged from 22 to 72 years (mean, 57 years). Histological grading of these patients yielded 26 grade 1 tumors, 33 grade 2 tumors, and 1 grade 3 tumor. In all, 27 of these subjects had stage I disease, 23 had stage II disease, 7 had stage III A disease, 2 had stage III B disease, and 10 had stage III C disease (Table 1).

There was no difference in the distribution of either histological grade or disease stage between the patients who received VAU therapy and the untreated control group as determined using the chi-square test. The postoperative observation period ranged from 7 to 16 years (mean, 10 years). Survival values were calculated by the Kaplan-Meier method, and significant differences were tested by the log-rank test and the generalized Wilcoxon test.

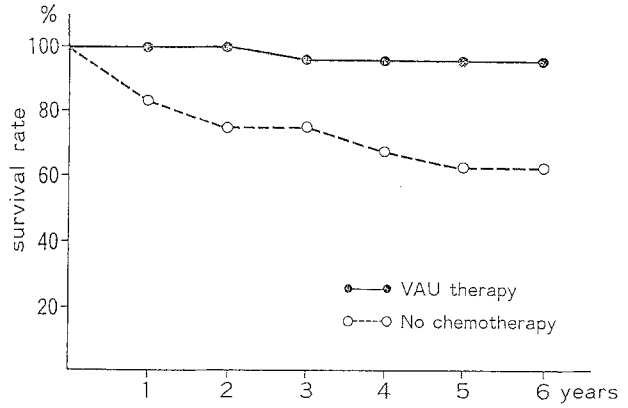

Fig. 1. Survival of patients with stage I–III renal-cell carcinoma

Table 1. Features of the renal-cell tumors in treated and control patients

	Stage			Grade		
	I	II	III	1	2	3
VAU therapy	15	10	6	14	17	0
No chemotherapy	27	23	10	26	33	1

Table 2. VAU regimen

Drug	Dose	Administration schedule
VLB	5 mg/m^2	i. v. every 4 weeks for 5 courses
ADM	30 mg/m^2	i. v. every 4 weeks for 5 courses
UFT	3 capsules	p. o. daily for 2–3 years

Table 3. Side effects of VAU therapy

Side effect	Number of cases
Alopecia	25 (81%)
Gastrointestinal toxicity	13 (42%)
Anorexia	11
Nausea and vomiting	4
Diarrhea	2
General fatigue	5 (16%)
Hematological toxicity	11 (35%)
Leukopenia	11
Thrombocytopenia	0

Results

Relapse and metastasis

Only 1 (3.2%) of 31 patients experienced postoperative relapse and metastasis. This subject had stage II disease and showed grade 2 histology, and metastasis developed in the left humerus at 6 months postsurgery.

Survival

Thus far, 30 of 31 patients have survived without suffering a relapse during the postoperative observation period ranging from 2 years and 6 months to 7 years and 1 month after surgery. The 1-year survival of our subjects was 100%, and the 3- and 5-year survival values were 96%. These results were significantly better (P <0.01) than the respective values (81%, 72%, and 60%) obtained for the historical controls (Fig. 1). The above-mentioned patient who experienced a relapse died at 2 years and 7 months postsurgery.

Side effects

The most frequently encountered side effect of VAU therapy was alopecia, which occurred in 25 (81%) of 31 patients (Table 3). However, this condition was reversed in all cases after the administration of VLB and ADM had been completed. One or more gastrointestinal symptoms such as anorexia, nausea, and vomiting were observed in 13 subjects. All of these symptoms were transient and mild, and in no case did they require the discontinuation of treatment. The hematological examination revealed a decrease in the leukocyte count to less than 3,000/mm^3 in 11 patients (35%), but no subject showed a WBC of less than 1,000/mm^3. The leukopenia was attributable to VLB and ADM, as it did not occur during the administration of UFT alone after the completion of VLB and ADM treatment. On the other hand, no patient showed a platelet count of less than 100,000/mm^3. No hepatic or renal dysfunction occurred.

Discussion

No especially effective anticancer agent for renal-cell carcinoma has yet been found. Even VLB, whose use has thus far produced the best results, yields an efficacy rate of only about 15% [1, 3]. Thus, there have been very few reports of distinct improvement in the survival of patients due to the use of postoperative adjuvant chemotherapy for renal-cell carcinoma.

UFT is a preparation consisting of tegafur and uracil mixed at a molar ratio of 1:4, and one capsule contains 100 mg tegafur and 224 mg uracil. This formulation was prepared on the basis of the finding that uracil suppresses the decomposition of 5-fluorouracil and elevates the antitumor effect of the latter by increasing the tumor drug level. The level of 5-fluorouracil in the tumor rose more markedly than did the serum drug concentration when the molar ratio was 1:4 [2]. We have recently given UFT to 22 patients with progressive renal-cell carcinoma and obtained an efficacy of 32% (7/22 subjects) [5]. Similarly satisfactory results have been reported by other institutions [4].

In the present study, we used the VAU regimen in 31 patients with stage I, II, or III renal-cell carcinoma whose tumors were considered to have been completely resected surgically and assessed its effectiveness. The re-

sults obtained in our patients (1-year survival, 100%; 3-year survival, 96%; and 5-year survival, 96%) were significantly more satisfactory than the corresponding 81%, 72%, and 60% values achieved by the 60 subjects who served as historical controls ($P < 0.01$). In the literature as well, the 5-year survival values obtained in patients with stage I, II, and III disease were 65%–82%, 47%–64%, and 31%–51% respectively, [6–8]. Therefore, postoperative VAU therapy might be effective in improving the prognosis for this disease. Further improvement in the homogeneity of the patients' features would require that larger numbers of patients be examined prospectively over longer periods.

Alopecia, gastrointestinal symptoms, and leukopenia were encountered during the therapy, but they were transient or mild. Most of these side effects were considered to be attributable to VLB and ADM, since the long-term use of UFT never became problematic.

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