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Combination Chemotherapy with Fluorouracil, Adriamycin, *cis*-Platinum and VM-26 in Advanced Transitional Cell Carcinoma of the Urinary Tract

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Abstract—*From October* 1981 *to October* 1984, 42 *consecutive patients with locally advanced unresectable or metastatic transitional cell carcinoma of the urinary tract were treated with* cis-*Platinum* 50 mg/m^2 *i.v. and Adriamycin* 50 mg/m^2 *i.v. day* 1, *and Fluorouracil* 500mg/m^2 *i.v. and VM*26 100 mg/m^2 *days* 1 *and* 8, *every* 3 weeks. *In the* 36 *evaluable patients,* 4 *complete remissions and* 15 *partial remissions were noted* (52.7% *response rate*). *Of the* 12 *patients with previously untreated, locally advanced bladder carcinoma,* 8 *responded, with* 3 *pathologically confirmed complete remissions. Toxicity was moderate. Median survival was* 44 *weeks. This* 4*-drug combination had significant palliative activity in our patient population. Its role in the preoperative setting deserves further evaluation.*

INTRODUCTION

In the past few years several chemotherapeutic agents have proven useful in the management of advanced transitional cell carcinoma of the urinary tract (TCCUT). The most effective agent, with a reported 33% response rate is *Cis*-Platinum (DDP); other drugs, such as Cyclophosphamide, Methotrexate, Adriamycin (ADM) and Fluorouracil (FU) have shown activity in this disease [1]. The role of VM-26 is more uncertain; however, a 17% response rate was noted in early studies by the EORTC [2]. Several drug combinations have yielded a 40–60% response rate [1], although the superiority of combination chemotherapy over DDP has not been demonstrated in randomized trials. The combination of ADM and FU induced in our hands a 35% response rate in patients with bladder carcinoma [3]. In October 1981, a prospective phase II study was started at our Institution with the aim to evaluate the efficacy and the toxicity of a new regimen resulting from the addition of DDP and VM-26 to the combination of ADM and FU in advanced TCCUT. This article reports the results of that study.

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MATERIALS AND METHODS

From October 1981 to October 1984, 42 consecutive eligible patients (pts) with advanced TCCUT entered into the study.

Conditions of eligibility included: histologically proven transitional cell carcinoma of the bladder, renal pelvis or ureter; locally advanced unresectable and/or metastatic disease; no previous chemotherapeutic treatment; age less than 70 yr; performance status greater than 40; no concomitant antineoplastic treatment; serum creatinine $\leq$ 1.2 mg/dl, serum bilirubin $\leq$ 1.5 mg/dl, white blood cells counts $\geq$ 4000/nl, platelets counts $\geq$ 100.000/nl.

Staging procedures included clinical examination, routine laboratory tests, EKG, bone scintigram and chest X-rays in all pts, cystoscopy, bipedal lymphangiogram and CT scan studies when the primary tumor was still present.

Chemotherapy consisted of DDP 50 mg/m^2 i.v. and ADM 50 mg/m^2 i.v. day 1, and FU 500 mg/m^2 i.v.and VM-26 100 mg/m^2 i.v. day 1 and 8, every 3 weeks. On day 1 pts received 1.500 ml of i.v. fluids with 100 g of Mannitol.

Follow-up studies included complete blood counts before each administration of chemotherapy, serum creatinine before each administration of DDP and those tests indicated to define response every 2 cycles of chemotherapy. Other

diagnostic procedures were performed upon clinical indication.

In case of leuko-thrombocytopenia on day 1, a new cycle was delayed until bone marrow recovery, while on day 8 reduction criteria were employed as follows: for white blood cells counts between 3.000/nl and 4.000/nl and for platelets counts between 70.000/nl and 100.000/nl half doses of FU and VM-26 were administered, while for lesser values chemotherapy was not given.

In case of elevation in serum creatinine, DDP was discontinued until normalization.

Response and toxicity were classified according to the World Health Organization criteria [4].

Survival was calculated according to the life-table method.

Of the 42 pts treated, 40 were males, 2 females. Median age was 65.5 yr (range 38–74). All pts had bladder carcinoma except 2 with metastatic ureteral carcinoma and one with metastatic renal pelvis carcinoma.

In 18 pts disease was limited to the pelvis (previously untreated bladder carcinoma in 15 pts, pelvic relapse after radical cystectomy, partial cystectomy and radiotherapy in 1 pt each), while in 24 metastatic disease was present (bone in 10 pts, lungs in 7, iuxtaregional lymphonodes in 13, skin in 1). The median number of sites involved was 1 (range 1–4). Twenty-five pts were not pretreated, 11 had undergone radical surgery, 5 radiotherapy.

RESULTS

Of the 42 pts entered into the study, 6 were considered not evaluable for response and 2 for toxicity. Reasons for unevaluability included early death in 3 pts, loss to follow-up in 2, treatment refusal due to toxicity in 1. A total of 129 cycles was administered to the 36 evaluable pts. Median number of administered cycles was 3. Four complete remissions (CR), 15 partial remissions, 7 stable disease and 10 progressions were noted. Response rate (responding/evaluable pts) was 52.7%. If the 3 pts with early death are included, response rate was 48.7%. Of the 12 pts with previously untreated, locally advanced bladder carcinoma, 8 responded, with 3 pathologically confirmed CR at subsequent radical cystectomy performed in 4 pts (1 pt had undergone pre-surgery RT).

Response was noted in 1/3 pts with pelvic relapse after local treatment, 3/5 with pulmonary metastases, 4/9 with osseous metastases, 0/1 with skin metastases, 6/12 with lymphonodal metastases.

In 11/19 responding pts subsequent local treatment (radiotherapy or surgery) was employed. Median duration of response to chemotherapy alone was 26 weeks (17–34). Median duration of response to the whole treatment was 57.5 weeks (18–234.5+).

Toxicity was moderate. Nineteen pts experienced leuko-thrombocytopenia (grade 3–4 in 2 pts), 10 grade 3–4 nausea and vomiting, 4 grade 1 reversible elevation in serum creatinine.

It was possible to administer a median of 92% of the calculated dose for ADM, 75.5% for DDP, 88% for FU and 86.5% for VM-26. No toxic deaths were encountered.

Survival curve (all eligible pts) is reported in Fig. 1. Median survival was 44 weeks, with 9 pts still surviving.

DISCUSSION

When this study was initiated, the literature regarding the chemotherapy of advanced TCCUT consisted of several phase II studies exploring the activity of single agents and chemotherapy combinations. There was an indication that a combination chemotherapy could yield better response rates than single agents and interesting results had been published with combinations of Cyclophosphamide, ADM, Methotrexate, FU and DDP [5].

Following our previous experience with ADM and FU [3], it was decided to expand it to the 4-drug combination reported in this paper. The drugs employed had been reported as active and the expected toxicity was only partially superimposable. It should be noted that further studies [5] have questioned the activity of VM-26 in advanced bladder cancer and that the relative role of this drug in our combination is uncertain.

In Table 1 the results obtained by several groups in phase II studies are reported. When our results in terms of response rate are compared to those previously reported, they seem to be comparable. In particular, various combinations of DDP with the other drugs included in the regimen employed

Table 1. Activity of chemotherapy combinations in advanced urothelial carcinoma

Drugs	No. patients	Response rate (%)	Ref.
DDP+ADM	40	53	6
DDP+ADM+FU	39	46	7
DDP+MTX+VLB	37	57	8
DDP+CPM+ADM	42	40	9
DDP+VM26	41	51	10
DDP+MTX	43	46	11
DDP+ADM+MTX +VLB	45	67	12
DDP,+FU,+ADM, +VM26	36	53	Present series

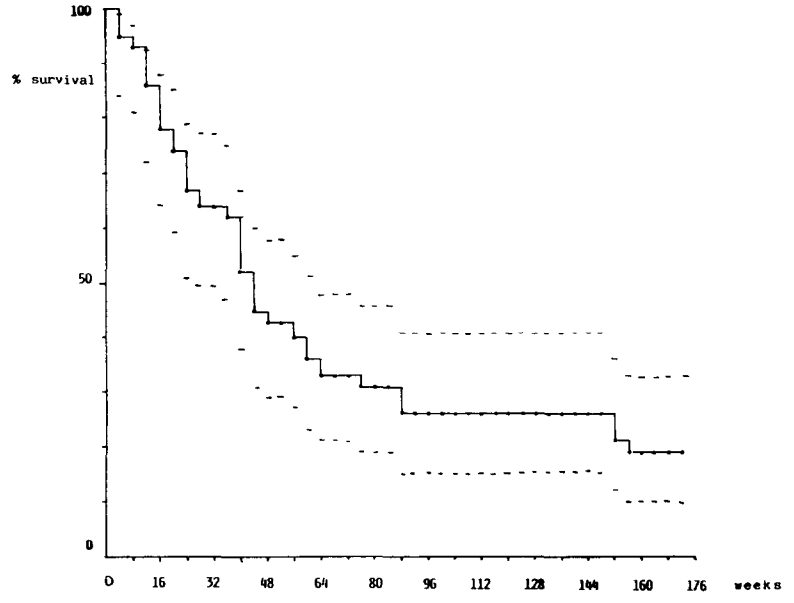

Fig. 1. Overall survival of all eligible pts and 95% confidence interval.

by us had comparable activity. In contrast, the addition of MTX to DDP was found recently to be capable of increasing CR rate, even if at the expense of a greater toxicity [8, 11, 12].

Recently, some cooperative randomized studies have been reported. In the SWOG study, DDP+ADM proved superior to ADM alone [13]. The study from the NBCCGA [14] failed to show a greater activity of the combination of CTX and DDP than DDP alone. However, response rate was very low in both arms (12 and 20% respectively), suggesting the presence of subtly unfavorable prognostic factors. In another recent randomized study from the ECOG, comparing the combination of Cyclophosphamide, ADM and DDP to DDP, higher response rates were noted with a nearly double, albeit not significant, response rate in the combination arm. Survival showed a marginal, non-significant benefit for the combination. DDP seems therefore essential for the activity of a combination, and also ADM seems to be a drug worth being included in future combinations to be compared to DDP alone.

Toxicity was moderate in our study, with 30% of pts presenting grade III–IV toxic effects and a 75–92% of the calculated dose administered. Similarly to efficacy, toxicity is roughly superimposable to that previously reported in phase II studies; however, the exclusion of Methotrexate from our combination prevented the inconveniences caused by the interaction of this drug with DDP.

An interesting point in our material is the presence of a high response rate and of pathologically confirmed complete responses when FADV is used preoperatively in patients with T_3–T_4 disease. These results are in accordance with those noted by other groups [12, 16, 17] and have led us to start a prospective chemotherapeutic–surgical pilot study.

In conclusion, the FADV combination yielded in our hands a substantial response rate, particularly in patients with previously untreated, locally advanced bladder cancer; whether it is more effective than DDP alone remains to be studied.

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REFERENCES

1. Torti FM, Harker GW. Chemotherapy of advanced transitional cell carcinoma of the uroepithelium. *Cancer Chemother Pharmacol* 1983, **11,** 1–4.
2. Pavone-Macaluso M and EORTC. Genitourinary Tract Cooperative Group A: Single drug chemotherapy of bladder cancer with Adriamycin, VM-26, or Bleomycin. A Phase II multicentric cooperative study. *Eur Urol* 1976, **2,** 138–141.
3. Veronesi A, Magri MD, Figoli F, Tirelli U, Galligioni E, Trovo MG, Merlo A, Dal Bo V, Tumolo S, Grigoletto E. Combination chemotherapy with Adriamycin and 5-Fluorouracil in advanced bladder carcinoma. *Clin Oncol* 1982, **8,** 103–106.
4. Miller AB, Hoogstraten B, Staquet M *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47,** 207–214.

5. Yagoda A. Chemotherapy of bladder cancer. *Cancer* 1980, **45,** 1879–1888.
6. Yagoda A. Phase II trials in patients with urothelial tract tumors. *Cancer Chemother Pharmacol* 1983, **11,** 9–12.
7. Williams SD, Einhorn LH, Donohue JP. Cisplatin combination chemotherapy of bladder cancer. *Cancer Clin Trials* 1979, **2,** 335–338.
8. Harker WG, Freiha FS, Shortliffe LD, Meyers FJ, Hannigan JF, Flam MS, Torti FM. Cisplatin, Methotrexate and Vinblastine (CMV) chemotherapy for metastatic transitional cell carcinoma of the urinary tract: evaluation of complete response by site. *Proc Am Soc Clin Oncol* 1984, **3,** 160.
9. Mulder JH, Fosså SD, De Pauw M, Van Oosterom AT. Cyclophosphamide, Adriamycin and Cisplatin combination chemotherapy in advanced bladder carcinoma: an EORTC Phase II Study. *Eur J Cancer Clin Oncol* 1982, **18,** 111–112.
10. Stoter G, Van Oosterom AT, Mulder JH, De Pauw M, Fosså SD. Combination chemotherapy with Cisplatin and VM-26 in advanced transitional cell carcinoma of the bladder. *Eur J Cancer Clin Oncol* 1984, **20,** 315–317.
11. Stoter G, Fosså SD, Klein JGM, Denis L, Splinter T, Jones WG, Keizer J, Sylvester R. Combination chemotherapy with Cisplatin (DDP) and Methotrexate (MTX) in advanced bladder cancer. An EORTC Phase II study. *Proc Soc Clin Oncol* 1985, **4,** 106.
12. Sternberg CN, Yagoda A, Scher HI, Watson RC, Hollander PS, Herr HW, Sogani PC, Morse MJ, Fair WR, Whitmore WR. M-VAC: Update of Methotrexate (MTX), Vinblastine (VLB), Adriamycin (ADM), and Cisplatin (DDP) for urothelial tract cancer. *Proc Soc Clin Oncol* 1985, **4,** 105.
13. Gagliano R, Levin H, El-Bolkainy M *et al.* Adriamycin versus Adriamycin plus cis-Diamminedichloroplatinum (DDP) in advanced transitional bladder carcinoma. *Am J Clin Oncol* 1983, **6,** 215–218.
14. Soloway MS, Einstein A, Corder MP, Bonney W, Prout GR, Coombs J. A comparison of Cisplatin and the combination of Cisplatin and Cyclophamide in advanced urothelial cancer. *Cancer* 1983, **52,** 767–772.
15. Khandekar JD, Elson PJ, Diwys WD, Slayton RE, Harris DT. Comparative activity and toxicity of *cis*-Diamminedichloroplatinum (DDP) and a combination in disseminated transitional cell carcinoma of the urinary tract. *J Clin Oncol* 1985, **3,** 539–545.
16. Raghavan D, Hedley D, Phillips J, Rugg C, Pearson B, Duval P, Watt WH. 50 patients treated with first-line intravenous Cisplatin for deeply invasive ($T_{3-4}N_xM_0$) bladder cancer: response rate, survival and flow cytometry. *Proc Am Soc Clin Oncol* 1984, **3,** 157.
17. Fagg SL, Dawson-Edwards P, Hughes MA, Latief TN, Rolfe EB, Fielding JWL. *Cis*-diamminedichloroplatinum (DDP) as initial treatment of invasive bladder cancer. *J Urol* 1984, **56,** 296.