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Phase-II trials in patients with urothelial tract tumors

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Summary. *Major progress has been made in the treatment of patients with advanced urothelial tract tumors, using a systematic phase II approach in selected patients. At this time, DDP and MTX, singly, seem to induce the largest number of responses, while VLB and ADM, singly, are good secondary agents. The combinations of DDP + ADM, and VLB + MTX appear to be somewhat more effective than the single drug components, and hopefully a four-drug combination may be even more effective. Since significant antitumor activity is achieved with the drugs now available, we plan to initiate a randomized phase-III study in patients with stage-D tumors after preoperative irradiation and radical cystectomy with lymph node dissection. The data at Memorial Sloan-Kettering Cancer Center indicate a 70% death rate at 1 year, and 87% at 2 years, despite radiation therapy and cystectomy; for such cases, therefore, chemotherapy may be useful in prolonging survival. While new drugs still need to be defined, transitional cell carcinoma of the urothelial tract must be considered a tumor responsive to chemotherapy; we may possibly be on the threshold of chemotherapeutically curative therapies.*

In 1975, after a review of previous chemotherapy studies in urothelial tract tumors at Memorial Sloan-Kettering Cancer Center, a systematic approach was adopted to more accurately define of the efficacy of cytotoxic drugs through the mechanism of standard phase-II trials. Certain, rather rigid, requirements were needed: (1) a selected patient population with bidimensionally measurable lesions to allow definition of a clear end-point of response; (2) a concise and readily acceptable definition of response criteria with exclusion of minor response (MR), stabilization of disease (STAB), and mixed response from the overall 'objective' response rate; (3) an independent evaluation of all radiologic findings with a final review of each case, upon protocol completion, clearly separating 'measurable' from 'evaluable' cases; and (4) a recognition of the need to enter patients with a good Karnofsky performance status (KP) and a history of minimal prior irradiation and chemotherapy so that adequate doses could be administered [7].

Table 1 lists the bidimensionally measurable parameters required for such phase-II trials. Prior to the availability of computerized transaxial tomography, lymphangiography and surgical clips circumferentially placed around the tumor mass had been employed to measure intra-abdominal lesions [7, 9–11]. However, both techniques have been discontinued because of inaccuracies on repeated measurements. For similar reasons, changes in intra-abdominal and pelvic masses as judged on physical examination or digital rectal examination, which were considered acceptable initially as measurements of lesions and required a > 75% reduction in tumor size for response, are categorized now as 'evaluable' parameters [8, 13]. Radionuclide bone scans, roentgenographic skeletal surveys, intravenous pyelography and sonography of intra-abdominal and pelvic masses, and unidimensional hilar masses on chest X-ray, rectal masses on digital rectal examination, and intra-abdominal masses on physical examination are considered to be relatively imprecise parameters for phase-II trials [7, 8, 13].

Table 1. Patient selection criteria

Measurable indicator lesions:
Bidimensional lymph nodes by physical examination or CT scan
Cutaneous masses
Subcutaneous masses
Pulmonary metastases; peripheral by X-ray or by CT scan
Hepatic masses by physical examination,
+ radionuclide scan ± CT scan
Abdominal/pelvic masses by CT scan
Evaluable lesions:
Unidimensional osseous lesions by X-ray or radionuclide scan
Abdominal/pelvic masses by physical examination
Biochemical abnormalities
Hepatic masses by physical examination only
Hilar pulmonary lesions

Response criteria are outlined in Table 2. The category complete remission (CR) is used infrequently, because of previous experience in a limited number of cases in which, at laparotomy, gross residual disease was found despite a negative diagnostic work-up. Thus, in the protocols at Memorial Hospital, most patients are simply listed as achieving partial remission (PR) [7]. If the carcinoembryonic antigen (CEA) is abnormally elevated, which occurs in approximately 50%–60% of cases, a major (> 50%) reduction of this is also required. However, the CEA alone, without bidimensionally measurable lesions, is insufficient to classify patients as 'measurable'. In the majority of clinical trials, patients who achieve MR status seem to be either progressors/stabilizers or responders (PR) in whom all tumor measurements simply do not add up to > 50%. Occasionally, some patients with MR status have had response persist as long as or longer than the median time interval for patients who achieve CR/PR status. Such patients have probably achieved PR status but are still

Table 2. Response criteria

CR	Complete remission: Disappearance of all measurable, radiologic and biochemical abnormalities, including osseous lesions, clinically
PR	Partial remission: Soft-tissue lesions − > 50% decrease in the summed products of the longest and perpendicular diameters of all lesions for > 1 month, measured by physical examination, X-rays, radionuclide liver scans, and CT scans; Hepatomegaly: > 50% decrease in the sum of all available measurements by physical examination and a > 50% decrease in all biochemical abnormalities including any biologic marker (i.e., CEA, beta HCG)
MR	Minor response: A 25%−49% decrease in tumor parameters as per PR for > 1 month or a PR of < 1 month duration
STAB	Stabilization of disease: A 25% decrease or increase in tumor size or biochemical abnormalities for more than 3 months
PROG	Progression: A > 25% increase in tumor size or biochemical abnormalities; appearance of new lesions; mixed response

classified as MR. In addition, patients who have STAB frequently have had a long 'lead time' (course of disease), i.e., diagnosis to metastases and metastases to protocol, and are thus relatively slow progressors rather than stabilizers.

Although X-rays and CT scans are examined routinely during the trial, all so-called responders and stabilizers are reviewed independently by Dr R. C. Watson, Chief, Diagnostic Radiology, Memorial Hospital. Review generally occurs 2 months after completion of the trial. In addition, all equivocal lesions are evaluated and classified at that time as measurable or evaluable. All peripheral lesions ascertained by physical examination are measured by at least two observers utilizing the longest and their perpendicular diameters. Karnofsky performance status is used for evaluation of subjective parameters. At Memorial Hospital, leukopenia and thrombocytopenia are defined as a white blood cell count < 4,000 and a platelet count < 150,000. In all instances, in each trial the percentage of patients who have myelosuppression and the median nadir and range of thrombocytopenia and leukopenia are listed.

Table 3 outlines the most frequently employed doses and schedules for each protocol. Dose modifications were necessary because of extensive prior irradiation or chemotherapy, and the original articles for the latter protocols should be reviewed for such modifications.

Protocols I, II, V, and VI evaluated doxorubicin (ADM) alone and in combination with cyclophosphamide (CTX), cisplatin (DDP), and both drugs together. Two ADM schedules were used, but the majority of cases received the single-dose bolus schedule every 3 weeks [10]. Response occurred in 17% of cases (Table 4), being observed usually after the second or third dose and persisting for 3−6 months [10]. While initial reports suggested a remission rate for ADM of 35%, subsequent studies described complete and partial remissions in only 17% of cases. In protocol II, the addition of cyclophosphamide was not synergistic [11].

Cisplatin, used singly in doses of 1.6 mg/kg or 70 mg/m^2, induced remission in 40% of unpretreated cases, and in 33% of all patients at Memorial Hospital [9, 13]. Almost all responses were evident within 7−28 days and none started after two doses. The duration of remission was 3−6 months, but many patients either refused therapy because of intolerable nausea and vomiting, or experienced renal dysfunction which precluded additional doses [8]. Despite the report by Soloway and co-workers of potential synergism of DDP and CTX, in a highly selected patient population at Memorial Hospital, no synergistic or additive effects (protocol IV) were observed (Table 4) [12].

Table 3. Doses and schedules used for each protocol

Protocol no.	Drug(s)	Doses (mg/m^2)	Frequency
I	ADM	30, 45, 60	Every 3 weeks
II	ADM	45−60	Every 3−4 weeks
	CTX	450−600	
III	DDP	70	Every 3 weeks
IV	DDP	70	Every 3−4 weeks
	CTX	500−750	
V	DDP	70	Every 3−4 weeks
	ADM	45	
VI	DDP	70	Every 3−4 weeks
	CTX	250	
	ADM	30−45	
VII	MTX	40	Weekly
VIII	VLB	0.10−0.15 (mg/kg)	Weekly
IX	VLB	4	Weekly
	MTX	40	
X	NCS	2,000−2,500 units × days	Every 6−8 weeks
XI	PALA	3,000−4,500	Weekly
XII	AMSA	90−120	Every 3 weeks
XIII	Bisantrene	280	Every 3 weeks
XIV	DAAM	37.5	Weekly
XV	DACCP	640	Every 3 weeks
XVI	Methyl-G	400−600	Weekly

Table 4. Results of chemotherapy trials in advanced urothelial tract cancer at Memorial Sloan-Kettering Cancer Center

Protocol no.	Drug(s)	Adequate patients		Pre-treated		Unpre-treated	
		n	% CR/PR	*n*	% CR/PR	*n*	% CR/PR
I	ADM	44	16	24	13	20	20
II	ADM + CTX	18	17	6	17	12	17
III	DDP	56	30	18	11	38	40
IV	DDP + CTX	34	44	7	43	27	44
V[a]	DDP + ADM	40	53	10	50	30	53
VI	DDP + CTX + ADM	28	46	2	50	26	46
VII	MTX	42	26	26	19	16	38
VIII	VLB	26	16	19	15	9	22
IX[a]	VLB + MTX	40	38	9	11	31	45
X	NCS	19	5	13	0	6	17
XI	PALA	17	0	17	0	0	0
XII	AMSA	21	10	19	11	2	0
XIII[a]	Bisantrene	12	0	–	–	–	–
XIV[a]	DAAM	4	25	–	–	–	–
XV[a]	DACCP	4	25	–	–	–	–
XVI[a]	Methyl-G	4	0	–	–	–	–

[a] Trials in progress

When DDP is combined with ADM, and with ADM and CTX, the overall response rate increases to 53% and 46%, respectively, and the duration of response also increases [8, 13; S. Schwartz et al. 1983, unpublished work]. With the three-drug combination, the median survival time for responders is 21 months, vs 9 months for nonresponders. The response rate of DDP at Memorial Hospital for all cases is 30% with 95% confidence limits of 18%–42%, and for the previously untreated cases, 40% with 95% confidence limits of 24%–56%. The three-drug combination response rate is 46% with 95% confidence limits of 28%–64%. When DDP is compared with DDP + ADM + CTX (30% vs 46%), the P value is only 0.16. However, when the response rate in the literature is examined, 46% (95% confidence limits, 39%–53%) of 202 cases given DDP + CTX + ADM responded vs 31% (95% confidence limits, 26%–36%) given DDP alone ($P = 0.0002$) (S. Schwartz et al. 1983, unpublished work). Recent data obtained with protocol V suggest no additive effect with CTX: DDP and ADM seem to be the active components.

The number of cases of responders to ADM alone and to DDP alone are few, yet no difference was found with ADM in improving the quality of life, as measured by the Karnofsky performance scale. However, statistically, there is improvement with DDP (Table 5). When response rates are examined for protocols I, II, and I + II vs III, IV, and III + IV, the DDP regimens are superior (Table 6). Similarly, the DDP regimens induce a significant prolongation in survival compared with ADM regimens (Table 7), and DDP responders (PR) survive significantly longer than non-responders (PROG) (Table 8).

Previous experience at the Royal Marsden Hospital in England with methotrexate (MTX) for local T_{3-4} lesions led to a trial of this drug in patients with advanced disease [3]. The dose and response rate are listed in Tables 3 and 4. Response occurred after two to four doses and rarely started after six weekly doses. The duration of response was 5–7 months, similar to that achieved with DDP. Vinblastine sulfate (VLB) had never been evaluated for treatment of transitional cell carcinoma, and in a heavily pretreated patient population was found to have a remission rate similar to that of ADM used singly [1]. Responses occurred after four to six doses but persisted for only 3–5 months in this selected patient population. Protocol IX has not yet been completed, but preliminary results indicate a minor additive effect with combination of the two agents [6]. A randomized trial of MTX + VLB vs MTX will be required to define the efficacy of the two-drug combination more accurately.

Four other agents have been used, mostly in previously treated cases: neocarcinostatin (NCS) [2], 4′-9-acridinylaminomethane sulfon-m-aniside (AMSA) [4], *N*-phosphonoacetyl L-aspartic acid (PALA) [5], and 9,10-anthracenedicarboxyldehyde bis-4,5-dihydro-*H*-imidazol-2-yl-hydrazone dichloride (bisantrene). No or, at best limited, antitumor activity was exhibited by any these agents when used in previously treated cases. Three new drugs, 10-deaza-aminopterin (DAAM), methylglyoxal-bis (guanylhydrazone) (Methyl-G), and a new platinum derivative, 1,2-diaminocyclohexane-(4-carboxyphthalato) platinum II (DACCP), are being evaluated, but the limited results are too early for any conclusion.

Another area of investigation at Memorial Hospital is the use of DDP 70 mg/m^2 on day 2 of a 5-day 400 rad/day preoperative irradiation protocol prior to cystectomy. Of 24 cases, six proved to be inoperable. However, tumor downstaging ($P < T$), was noted in nine (38%) cases, with 21% achieving P_0 status. A comparison of these results with a similar but non-randomized group of patients who refused such therapy reveals the incidence of downstaging to be significantly increased.

Table 5. Karnofsky performance scale (%): DDP

	Baseline	Last reported	Differences	
PR				
Median	85	90	+ 5	
Range	(70–100)	(80–100)	(0–20 +)	
PROG				$P \leq 0.002$
Median	70	40	− 40	
Range	(50–80)	(0–90)	(−50–10+)	

Table 6. Bladder cancer treated in the Memorial Sloan-Kettering Cancer Center: no prior therapy

	Patients no.	% CR/PR
DDP	38	40
ADM	20	20
DDP + CTX	27	44
ADM + CTX	12	17
DDP + DDP/CTX	65	42
ADM + ADM/CTX	32	19

Table 7. Bladder cancer: survival

	All cases		All unpretreated		PR's unpretreated	
	Weeks	*P*	Weeks	*P*	Weeks	*P*
DDP	27		31		64	
vs		0.22		0.08		0.0001
ADM	18		18		19	
DDP + CTX	25		25		35	
vs		0.60		0.79		0.89
ADM + CTX	25		25		46	
DDP	27		31		64	
vs		0.72		0.46		0.64
ADM + CTX	25		25		46	

Table 8. Bladder cancer: survival of responders vs progressors

	PR weeks	vs PROG weeks	*P*
ADM			
All cases	19	17	0.64
Unpretreated	19	17	0.64
ADM + CTX			
All cases	68	23	0.15
Unpretreated	46	23	0.11
DDP			
All cases	60	18	0.0001
Unpretreated	64	22	0.00001
DDP + CTX			
All cases	55	19	0.0001
Unpretreated	35	19	0.01

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