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Methylglyoxal bis-Guanylhydrazone in Advanced Bladder Cancer

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ALTHOUGH there has been progress in the development of combination chemotherapy regimens for patients with advanced bladder cancer there is a need for new active agents [1–3]. Methylglyoxal bis-guanylhydrazone (MGBG) is a polyamine biosynthesis inhibitor which induced complete remission in patients with transitional cell carcinoma of the bladder in phase I trials with the agent [4].

46 patients with advanced metastatic transitional cell carcinoma of the bladder were entered into a phase II trial. Eligibility criteria included: histologically confirmed, bidimensionally measurable metastatic transitional cell carcinoma of the bladder; only one previous systemic chemotherapy or immunotherapy regimen (up to two previous intravesical chemotherapy or immunotherapy regimens were acceptable); patients could have had radiotherapy if the disease had progressed (if measurable disease existed outside the previous radiation field); patients had to have a SWOG performance status of 3 or less; white cells 3500/μl or more and platelets 100,000/μl or more; serum creatinine 177 μmol/l or less and serum bilirubin 34 μmol/l or less; and patients' informed consent.

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Table 1. Patients' characteristics

Entered	46
Total eligible (1 patient had no measurable disease)	45
M/F	34/11
Median age in years (range)	61 (40–80)
Performance status (SWOG)	
0	11
1	16
2	13
3	5
Previous therapy	
None	1
Radiation therapy + chemotherapy	15
Chemotherapy* or immunotherapy	29
No. of weeks of therapy	
<4	23
4	12
5–8	6
>8	2
Unknown (too early)	2
Best response achieved	
Complete	0
Partial	0
Stable disease	5
Progression	17
Assumed no response	19
No follow-up measurements	7
Early death	4
Refused further therapy secondary to toxicity	8
Too early	4

*Methotrexate + vinblastine + doxorubicin + cisplatin.

MGBG was administered weekly at 600 mg/m^2 as an intravenous infusion in 150 ml D5W or normal saline over 30 min or more. Dose escalations of 100 mg/m^2 were given if no toxicity was noted. Weekly doses were reduced by 100 mg/m^2 for severe (SWOG grade 3) toxicities. One course of therapy was defined as 4 weeks of MGBG. SWOG criteria were used to assess tumour response.

45 of the 46 patients entered were eligible (Table 1). 1 patient had no measurable disease. 20 of the eligible patients (44%) had at least one or more courses. There were no complete or partial responses. The exact 95% confidence interval of 0 out of 45 is 0–8%.

Toxicities in the study consisted of grade 3 (severe) or greater nausea and vomiting in 16% of patients, with 2 patients requiring admission. Grade 3 diarrhoea occurred in 9% of patients (1 admitted). 1 patient had grade 4 mucositis and 1 had a perforated diverticulum leading to death. Other grade 2 or greater toxicities included fatigue and weakness in 3 patients, hypoglycaemia in 2, hypotension (under 90 mmHg systolic) in 2, weight loss in 4 patients (1 lost 4.5 kg and 1 lost 7.7 kg), and anaemia in 8. Toxicities were so troublesome that 8 patients refused additional treatments (usually after only 1–3 doses).

Despite the protocol calling for failure on only one previous chemotherapeutic regimen it is clear the patient population was