haematuria. At cystoscopy the entire bladder mucosa was ulcerated and the bleeding was not controlled by diathermy. After transfusion of a total of 14 units of blood, a cystectomy was carried out. Histological examination of the bladder revealed no tumour but extensive oedema and focal erosion of the mucosa in keeping with the clinical diagnosis of haemorrhagic cystitis.

This case demonstrates two points of interest. Differential responses at a number of sites may follow chemotherapy, and in haematological malignancies are usually attributed to limited drug access to 'sanctuary sites', notably the central nervous system, the eye, and the testis. There is no evidence that the ovary enjoys such protection from cytotoxics and it must be presumed that the ovary contained drug-resistant lymphoma in this case. It is curious that this tumour did not disseminate during 2½ years without treatment. The time course and the severity of the haemorrhagic cystitis are also unusual. The dose of cyclophosphamide received was moderately high, but there was no haematuria during the patient's chemotherapy. Clearly, there must have been subclinical urothelial damage, but in series where comparable doses of cyclophosphamide have been followed by pelvic irradiation we have not found reports of bleeding requiring cystectomy [1, 2]. The combination of cyclophosphamide and pelvic irradiation, however sequenced, is potentially damaging to the bladder, and it may be appropriate to consider the use of mesna uroprotection in situations where cyclophosphamide-containing regimens are likely to be followed by pelvic irradiation.

1. Heyn R, Raney RB, Hays DM, *et al.* Late effects of therapy in patients with paratesticular rhabdomyosarcoma. *J Clin Oncol* 1992, **10**, 614–623.
2. Sell A, Bertelsen K, Andersen JE, Stroyer I, Panduro J. Randomised study of whole-abdomen irradiation versus pelvic irradiation plus cyclophosphamide in treatment of early ovarian cancer. *Gynaecol Oncol* 1990, **37**, 367–373.

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# Local Response and Long-term Results of Preoperative M-VAC Regimen in Regionally Advanced Transitional Cell Carcinoma of the Bladder

**Antoine S. Abi-Aad, Arnulf Stenzl, Robert Figlin and Jean B. deKernion**

WE REVIEWED retrospectively the effect of neoadjuvant M-VAC regimen in 17 patients with regionally advanced transitional cell carcinoma (TCC) (5T3, 12T4, 3N+) and evaluated the role of subsequent surgery on tumour control and long-term survival. Of the 17 patients 14 were male, the age of the patients ranged from 24 to 74 years with a mean of 58 years and the median Karnofsky performance status was 70. Chemotherapy was administered according to the regimen and schedule described by Sternberg *et al.* [1]. All patients received two initial courses followed by response evaluation (cystoscopy, bladder biopsies, and computer tomography scan of the pelvis). In the presence of complete response, one further course was administered followed by radical surgery. If partial response occurred, two additional M-VAC courses were given before proceeding with surgery.

Radical cystectomy was performed in all patients with no major complications. All patients were followed-up until death or for a minimum of 42 months (mean: 56, range 42–78 months). Tumour downstaging (T0, Ta, T1, CIS, N0) occurred in 4 (80%) of the 5 T3 patients, and in 3 (25%) of the 12 patients with T4 tumours.

Long-term survival with no evidence of disease was achieved in 5 out of 17 patients (30%), suggesting that this approach did not alter the ultimate course of the natural history of the disease. Although the best survival rate was achieved in those who responded locally (Table 1), this result is in contrast with the 5-year survival of 75% reported in a recent review of 147 patients [2].

Local clinical recurrence was not detected in any patient. However, 70% of the patients with downstaged cancers developed distant metastases; this figure is similar to that reported for advanced TCC of the urothelium treated with M-VAC regimen where 68% of complete response patients relapsed [3].

Although in this small series we could not identify any trend for improved survival with neo-adjuvant M-VAC chemotherapy, our observations suggest that this regimen can render locally

*Table 1. Results*

| No. of patients | Stage | | Current status* | Follow-up (months) |
|---|---|---|---|---|
| | Clinical | Pathological | | |
| 3 | T3 Nx | pT0 | NED | 48+ |
| | | pT1 | DOD | 12 |
| | | pTCIS† N+ | DOD | 16 |
| 2 | T3 N+ | pTCIS | AWD | 78+ |
| | | pTCIS | NED | 42+ |
| 10 | T4 Nx | pT0 | NED | 46+ |
| | | pTa | DOD | 28 |
| | | pT3 | NED | 50+ |
| | | pT3 | DOD | 6 |
| | | pT3 | DOD | 16 |
| | | pT3 CIS | DOD | 12 |
| | | pT3 N+ | DOD | 14 |
| | | pT3 N+ | DOD | 34 |
| | | pT4 | DOD | 23 |
| | | pT4 N+ | DOD | 10 |
| 1 | T4 N+ | pT3 | DOD | 8 |
| 1 | T4 Nx M+‡ | pT CIS | NED | 66+ |

*NED: no evidence of disease; AWD: alive with disease; DOD: died of disease. †CIS: carcinoma *in situ*. ‡Solitary pulmonary nodule resected before chemotherapy.

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advanced bladder cancer operable in most patients. By doing so patients may be spared potential local complications such as recurrent bleeding, irritative symptoms and pelvic pain.

1. Sternberg CN, Yagoda A, Scher HI, *et al.* Preliminary results of M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) for transitional cell carcinoma of the urothelium. *J Urol* 1985, **133**, 403–407.
2. Splinter TAW, Scher HI, Denis L, *et al.* The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. *J Urol* 1992, **147**, 606–608.
3. Sternberg CN, Yagoda A, Scher HI, *et al.* Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. *Cancer* 1989, **64**, 2448–2458.

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## Corrections

**The Defence for the U.K. DCIS Trial**—The first sentence of this paper (*European Journal of Cancer* 1993, **29A**, p. 430) should have read "The U.K. ductal carcinoma *in situ* (DCIS) trial started in May 1990, after a gestation period of 18 months, having been designed by a multidisciplinary committee." It was previously stated that the trial started in May 1991 after a gestation period of 36 months.

**The Economic Impact of 5-HT$_3$ Receptor Antagonists**—The following letter was originally published in *The European Journal of Cancer*, Vol. 29A, No. 8, p. 930. Unfortunately, a table unrelated to the letter was placed in the text. This has now been removed.

# The Economic Impact of 5-HT$_3$ Receptor Antagonists

## K. Cunningham, J. Hirsch and A. Freeman

JONES AND COLLEAGUES present data on the budgetary impact of the 5-HT$_3$ receptor antagonists [1]. However, their model makes no attempt to quantify the financial and resource benefits of using the 5-HT$_3$ receptor antagonists in terms of their enhanced efficacy and tolerability (i.e. the costs associated with caring for a patient experiencing emesis or the side-effects of conventional antiemetics). In this regard it is of particular interest that Jones *et al.* suggest that the use of the 5-HT$_3$ receptor antagonists is not justified over the delayed emesis period. They have ignored data in the literature that report good efficacy for oral ondansetron over this period [2–4], and show that it is superior to placebo and metoclopramide following cisplatin [5] and non-cisplatin [6] chemotherapy, respectively. Clearly, the role of the 5-HT$_3$ receptor antagonists over this period needs to be further defined; in particular, to quantify the additional benefits resulting from their enhanced tolerability and impact on patients' quality of life [7, 8]. Conventional antiemetics have a significant propensity for side-effects, e.g. extrapyramidal reactions and sedation which are associated with impaired quality of life. The lack of such side-effects with ondansetron enables patients to carry out normal daily activities at home or work.

The cost effectiveness of 5-HT$_3$ receptor antagonists in clinical practice can only be fully evaluated from a broader perspective. Limiting the scope of evaluation to drug acquisition costs ignores the financial consequences of treatment failure and side-effects.

1. Jones AL, Lee GJ, Bosanquet N. The budgetary impact of 5-HT$_3$ receptor antagonists in the management of chemotherapy-induced emesis. *Eur J Cancer* 1993, **29**, 51–56.
2. Roila F, Bracarda S, Tonato M, *et al.* Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. *Clin Oncol* 1990, **2**, 268–272.
3. Rosso R, Campora E, Cetto G, *et al.* Oral ondansetron (GR 38032F) for the control of acute and delayed cyclophosphamide-induced emesis. *Anticancer Res* 1991, **11**, 937–940.
4. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991, **27** (Suppl.1), S18–S19.
5. Gandara DR, Harvey WH, Monaghan GG, *et al.* Efficacy of ondansetron in the prevention of delayed emesis following high dose cisplatin (DDP). *Proc Am Soc Clin Oncol* 1990, **9**, abstract 1270.
6. Schmoll HJ. The role of ondansetron in the treatment of emesis induced by non-cisplatin-containing chemotherapy regimens. *Eur J Cancer Clin Oncol* 1989, **25** (Suppl.1), S35–S39.
7. Hirsch JD, Lee JT, Erapski R. Quality of life with intravenous ondansetron vs standard anti-emetic therapy in patients receiving emetogenic cancer chemotherapy. *Proc Am Soc Clin Oncol* 1992, abstract 1368.
8. Soukop M, McQuade B, Hunter E, *et al.* Ondansetron compared with metoclpramide in the control of emesis and quality of life during repeated chemotherapy for breast cancer. *Oncology* 1992, **49**, 295–304.