In 30 patients, progressive under MVAC, a response rate of 30% (all partial responses) was obtained with 5FU (750 mg/m^2 d1–d5) in combination with alpha-2a interferon (intramuscular injection daily during 5FU, then 3 times weekly) at 6-week interval. There was mild haematological toxicity but non-haematological toxicity was considerable (grade 2–3 mucositis 63%, diarrhoea 17%, neurological effects in 2 patients) [13].

The combination of 5FU, cisplatin and interferon as second line treatment in patients with advanced TCC of the urothelial tract is now under study by the EORTC GU group.

CONCLUSION

Better understanding of the biology of TCC is essential in the development of new approaches for the treatment of this disease. These may include dose intensification with support of haematological growth factors or stem cell infusion. New drugs should be tested and known drugs such as 5FU should be reconsidered in new applications.

1. Sidransky D, Frost P, Von Eschenbach A, *et al.* Clonal origin of bladder cancer. *N Engl J Med* 1992, **326**, 737–740.
2. Miyao N, Tsai YC, Lerner SP, *et al.* Role of chromosome 9 in human bladder cancer. *Cancer Res* 1993, **53**, 4066–4070.
3. Sarkis AS, Dalbagni G, Cordon-Cardo C, *et al.* Nuclear overexpression of p53 protein in transitional cell bladder carcinoma: a marker for disease progression. *J Natl Cancer Inst* 1993, **85**, 53–59.
4. Levine EG, Raghavan D. MVAC for bladder cancer: time to move forward again. *J Clin Oncol* 1993, **11**, 387–389.
5. Scher HI, Geller NL, Curley T, Tao Y. Effect of relative cumulative dose intensity on survival of patients with urothelial cancer treated with M-VAC. *J Clin Oncol* 1993, **11**, 400–407.
6. Logothetis C, Dexeus F, Sella A, *et al.* Escalated therapy for refractory urothelial tumors: methotrexate–vinblastine–doxorubicin–cisplatin plus unglycosylated recombinant human granulocytes macrophage stimulating factor. *J Natl Cancer Inst* 1990, **82**, 667–672.
7. Sternberg CN, de Mulder PHM, van Oosterom AT, *et al.* M-VAC chemotherapy and recombinant human granulocyte-macrophage colony stimulation factor (rhGM-CSF) in patients with advanced urothelial tract tumors. *Ann Oncol* 1993, **4**, 403–407.
8. Einhorn LH, Roth BJ, Ansari R, Dreicer R, Loehrer PJ. Vinblastine, ifosfamide and gallium (VIG) combination chemotherapy in urothelial carcinoma. *Proc Am Soc Clin Oncol* 1994, **13**, 229.
9. Roth BJ, Dreicer R, Einhorn LH, *et al.* Paclitaxel in previously untreated, advanced transitional cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group (ECOG). *Proc Am Soc Clin Oncol* 1994, **13**, 230.
10. De Wit R, Stoter G, Blanc C, Hubert S, Verweij J. Phase II study of first-time docetaxel (Taxotere) in patients with metastatic urothelial cancer. *Ann Oncol Proc ESMO 19*, 1994, **5**, 67 (abst).
11. Sadan S, Bajorin D, Amsterdam A, Scher H. Docetaxel in patients with advanced transitional cell cancer (TCC) who failed cisplatin-based chemotherapy: a phase II trial. *Proc Am Soc Clin Oncol* 1994, **13**, 244.
12. Huan S, Stewart DJ, Waterfield B, Aitken S. Biochemical modulation using 5-fluorouracil (5-FU) and high dose folinic acid (FA) in metastatic bladder cancer after MVAC failure. *Proc Am Soc Clin Oncol* 1994, **13**, 242.
13. Logothetis CJ, Hossan E, Sella A, *et al.* Fluorouracil and recombinant human interferon alpha-2a in the treatment of metastatic chemotherapy refractory urothelial tumors. *J Natl Cancer Inst* 1991, **83**, 285–288.

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Prostate Cancer: a Continuum of Controversy

L.J. Denis

PROSTATE CANCER in its natural course is a single biological process with an usually slow but constant growth. The symptomatic stage of the disease can be temporarily arrested by endocrine treatment, but data abound that the clinical stage and grade of the tumour as well as a number of prognostic factors define the outcome of the disease independent of a given treatment [1]. This situation leads to controversy in the management of the disease, and errors in treatment by omission or addition.

Other factors contribute to the controversy. These include a lack of consensus on the anatomy of the prostate, histopathological classification and risk factors, the absence of an indicator of invasion or metastatic potential, the variable response to endocrine treatment and, last but not least, the fact that prostate cancer incidence and mortality are at peak incidence in the sixth and seventh decade of life where they compete with other causes of morbidity and death.

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One basic fact stands out above all arguments. Prostate cancer is a leading cause of cancer mortality in men likely to assume endemic proportions in the near future [2]. One clinical fact is universally accepted. Prostate cancer once outside the prostate becomes an incurable disease and almost half of the afflicted men will die.

Efforts to reduce this sombre prospect are directed towards decreasing the incidence of the disease, earlier detection and screening for disease in a curable stage, and improvements in therapy. None of these prospects look likely to be solved in the near future. Epidemiological studies and prospective randomised trials aim to elucidate the enigma of the latent cancers. Studies are under way on the true clinical incidence of prostate cancer, its zonal distribution with different outcome and, most importantly, the synthesis of data with different grades of disease, producing mortality rates of 13, 13 and 66%, respectively [3]. It is still not clear if the demonstration studies on early detection in the US or the pilot programmes for a Pan-European population screening programme offer a panacea or Pandora's box. A consensus meeting on screening for prostate diseases

brought proponents from both sides together and resulted in a workshop summary that will form a stable base for future discussions [4]. Some committees on pathology, markers and treatment raised serious questions on, respectively, the overall accuracy and quality control, the standardisation of prostate specific antigen (PSA) and its reproducibility, and the overall morbidity of both radical prostatectomy and conforming radiotherapy. Clinical reality runs ahead of this cautious approach and the National Survey in the U.S.A. revealed that use of the PSA test increased from 5.1 to 66.4% and transrectal ultrasound (TRUS) from 0.9 to 19.7%. The increased early detection of localised tumour led to a resulting increase of radical prostatectomy from 7.3 to 20.3% [5], while the use of radiotherapy remained unchanged. The wealth of data provided by surgery established the principle that PSA has to be used in conjunction with digital rectal examination [6], and that surgery of impalpable and invisible tumours treated insignificant or minimal tumours, moderate tumours and advanced tumours in 26, 37 and 37%, respectively [7]. Results of radiotherapy treatment for localised disease compare well with surgery in the first 5–10 years for localised disease, with a resulting trend to minimise surgery above 70 years of age [8].

The progress made in diagnosis and treatment of localised prostate cancer is not reflected in metastatic disease. There is no doubt that primary hormonal treatment is indicated in symptomatic patients, and a tailored approach to the individual patient is justified [9]. Maximal androgen blockade has emerged as the best treatment to achieve response, and this treatment may increase survival in patients with minimal disease [10]. However, the most important message from the EORTC trial, from which these data were derived, is that prognostic factor analysis allows the separation of randomised patients in 3 cohorts with respectively 5.2, 2.7 and 1.6 years of survival [1].

The end stage of the disease in its hormone independent state has a poor prognosis. Innovative strategies for early stage are under evaluation, while improved palliative care for advanced disease remains a major challenge.

1. Denis LJ. Staging and prognosis of prostate cancer. *Eur Urol* 1993, **24**, 13–19.
2. Boyle P. The evolution of an epidemic of unknown origin. In Denis L, ed. *Prostate Cancer 2000*. Heidelberg, Springer, 1993, 5–11.
3. Barry M. Natural history of clinically localized prostate cancer. *Semin Surg Oncol* 1994, in press.
4. Denis L, Murphy GP, Schröder F. Report of the Consensus Workshop on Screening and Global Strategy for Prostate Cancer, Antwerp, 5–7 March, 1994. *Cancer* 1995, **75**, 1187–1207.
5. Jones GW, Mettlin C, Murphy GP, *et al.* Patterns of care for prostate cancer: results of a National Survey of 1984 and 1990. *Cancer* 1995, in press.
6. Catalona WJ, Richie JP, Ahmann FR, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6630 men. *J Urol* 1994, **151**, 1283–1290.
7. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathological and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994, **271**, 368–374.
8. Dearnaley DP. Radiotherapy of prostate cancer: established results and new developments. *Semin Surg Oncol* 1995, **11**, 46–49.
9. Denis L. Primary hormonal treatment. *Cancer* 1993, **71**, 1050–1058.
10. Denis LJ, Whelan P, Carneiro de Moura JL, *et al.* Goserelin acetate and flutamide versus bilateral orchidectomy: a phase III EORTC trial (30853). *Urology* 1993, **42**, 119–130.

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Controversies in Testicular Cancer Management

A. Horwich

TESTICULAR GERM CELL tumours continue to increase in incidence in developed countries, and epidemiological studies have identified testicular maldescent, early puberty and genetic predisposition [1] as important aetiological factors. The tumour is usually associated with carcinoma *in situ* of the germinal epithelium, and studies of the contralateral testis identify this lesion in a similar proportion of patients to those who develop a second contralateral germ cell tumour [2]. Since this confers a risk of malignant transformation of approximately 50% within 5 years, management options include orchidectomy, close surveillance or localised low dose radiation [3]. Carcinoma *in situ* cells share, with the majority of germ cell tumours, the unusual cytogenetic abnormality of an isochromosome 12p, and the analysis of 12q deletions may allow the identification of a candidate tumour suppressor gene [4]. However, more detailed analyses allow the detection of genetic differences between teratoma and seminoma, even at the *in situ* stage, suggesting that these tumour types may evolve separately rather than sequentially [5].

Seminoma is both radiosensitive and chemosensitive and cure rates are extremely high. Nevertheless, there is controversy over management of stage I disease. Traditional radiotherapy may be associated with a small risk of carcinogenesis and this has led to:

(1) Reduction of the radiation field size.

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