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Recent Developments in the Biology and Management of Advanced Bladder Cancer

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INTRODUCTION

TRANSITIONAL CELL carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract, accounting for 1% of all cancers. At presentation, 10% are already invasive and 90% are superficial papillary carcinomas, localised to the mucosa or lamina propria and may be treated by endoscopic resection, intravesical chemotherapy or immunotherapy with Bacillus Calmette-Guerin. Of these, 10% will also become invasive, and will infiltrate into the muscular layer or deeper, and may cause metastases to lymph nodes or distant organs.

BIOLOGY

A clonal origin of TCC has been suggested by Sidransky and associates [1]. They reported the loss of chromosome 9q allele in tumours at different localisations in the bladder and at different points in time. Genetic defects, such as loss of heterozygosity (LOH) of chromosome 9, have been reported in both superficial and infiltrating TCC [2], suggesting that inactivation of a supposed suppressor gene is an early and important step in multistep carcinogenesis. The putative suppressor gene is localised between 9q12 and 9q34 [1]. The gene for the ABH tissue antigen is also localised in the q arm of chromosome 9 and loss of this antigen is known to be a poor prognostic factor. In contrast to superficial TTC, invasive tumours also show allelic loss of chromosome 17p, and they also often contain mutations (overexpression) of the *P53* suppressor gene [3], suggesting that these are late events in bladder carcinogenesis. The three defects (LOH of chromosome 9, allelic loss of 17p and mutation of *P53*), found in the primary tumour are also detected in metastases, indicating that these changes precede metastatic disease [2].

TREATMENT

The standard chemotherapeutic treatment of advanced invasive bladder cancer is MVAC (methotrexate, vinblastine, doxorubicin and cisplatin). Although complete remission rates of 13–35% have been reported, the median survival time of 1 year is rather disappointing [4].

The combination of haematopoietic growth factors and dose intensification of MVAC may improve the outcome of patients with advanced TCC: a steep dose–response relationship appears to exist for cisplatin in urothelial tract tumours with an increasing proportion of responders with doses up to 35 mg/m^2/week [5]. Higher doses in combination with haematological growth factors seem to overcome resistance of TCC to normal dosed treatment schemes with response rates of 40% and acceptable toxicity [6]. Dose intensification of MVAC is feasible in combination with haematological growth factors and a relative dose intensity of 1.65, with 2.5 times the conventional dose for doxorubicin and cisplatin can be achieved. Haematological toxicity was the main problem with thrombocytopenia grade 3 to 4 from the fourth cycle [7]. A randomised trial of the EORTC will examine if dose intensification of MVAC is more advantageous than standard treatment.

Gallium nitrate is a metallic salt and was used by Einhorn and colleagues in combination with vinblastine (1.1 mg/kg d1–d2), ifosfamide (1.2 g/m^2 d1–d5), mesna and G-CSF in a dose of 300 mg/m^2 as a 24 h infusion (d1–d5) every 21 days. Of the 25 chemonaive patients treated, 20% showed a complete response with chemotherapy alone and 20% with chemotherapy and subsequent surgery. Twenty eight per cent had a partial response (response rate: 68%). There was one treatment related death. Grade 3–4 haematological toxicity (anaemia 44%; granulocytopenia 60%), temporary blindness, hypocalcaemia and renal failure were the toxicities reported [8].

Taxanes are a new class of chemotherapeutics which act by interference of the microtubuli system in an unique manner. They cause inhibition of cell division by formation of bundles of microtubuli. In a phase II trial, 26 chemonaive patients were treated with 250 mg/m^2 paclitaxel by a 24-h infusion every 21 days in combination with G-CSF. The median number of cycles was 4 (range 1–10). A complete response was reported in 19.2% of patients and a partial resonse in 23.0% (response rate: 42%). Main toxicities were alopecia, granulocytopenia grade 3–4 (19.2%), mucositis (11.5%) and neurological symptoms (11.5%) [9]. The other taxoid available, docetaxel, investigated in Rotterdam produced a response rate of 50% (3 CRs, 5 PRs) in 16 chemonaive patients in an ongoing first line phase II study [10].

In 11 MVAC pretreated patients, docetaxel 100 mg/m^2 in a 1-h infusion was given every 3 weeks. One patient (9.1%) showed a partial response. Anaemia, granulocytopenia and thrombocytopenia in combination with mucositis, alopecia, asthenia and peripheral neuropathy were the main toxicities [11]. Taxanes seem to be active in TCC and studies with combination regimens are awaited.

5-Fluorouracil (5FU) and high dose folinic acid were tested in 13 MVAC pretreated patients. The treatment scheme consisted of 300 mg/m^2 5FU and 200 mg/m^2 folic acid over 5 days. One patient showed a minor response. Toxicity included mucositis, diarrhoea, nausea and vomiting, central nervous system disturbances and haematological suppression (granulocytopenia with one death due to febrile neutropenia) [12].

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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.

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Prostate Cancer: a Continuum of Controversy

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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