TREATMENT OF BLADDER CANCER: THE PRESENT AND THE FUTURE

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SUMMARY

Bladder cancer is one of the most frequent tumours of the urinary tract and the treatment of this malignancy requires close co-operation between urologists and oncologists. The superficial disease is treated with good results with transurethral resections and local immunotherapy or chemotherapy. However, there is a considerable fraction of BCG-refractory tumours (30%) and progression to muscle-invasive cancer. New approaches such as BCG combined with low-dose interferon or recombinant BCG strains are promising but need to be explored in prospective trials. Better understanding of the tumour biology and immunology will probably make it possible select patients with a high risk of progressive disease and to tailor further therapy options.

The cornerstone of muscle invasive tumours treatment is radical cystectomy. The neoadjuvant chemotherapy is a promising option, especially in tumours invading deeply into the bladder wall or infiltrating the surrounding organs, but it require furthers confirmation of the results in phase III trials before introducing it as a standard treatment. However some leading centers have already implemented neoadjuvant chemotherapy in some selected groups of patients (eg. M.D. Anderson). Combined chemotherapy and modern 3-D conformal radiotherapy enable us to preserve the organ and the function of the bladder (bladder conserving therapy) and they are intensively studied in current trials.

In the near future molecular characterisation of individual tumours might help to choose a bladder conserving therapy or cystectomy adopted to a for particular patient. So far, four-drug regimen – MVAC has been widely used in metastatic and locally advanced disease. Recently, it was shown that a combination of gemcitabine and cisplatin (GC) is equally effective but less toxic. New chemotherapies tested in clinical trials include gemcitabine, taxanes and new-class drugs interfering with signal transduction. Individualization of established and experimental treatment options based on molecular tumour characteristics, such as p53 status will probably be the future of bladder cancer pharmacotherapy.

Key words: Bladder cancer, chemotherapy, immunotherapy, radiotherapy, gene therapy.

INTRODUCTION

In the European Union countries cancer of the bladder accounts for about 7% of all cancers in men [1] and its incidence has been the increase in almost all European populations [2]. The difference in incidence between sexes is mainly attributed to smoking habits and may also be associated with exposure to some carcinogens in the environment [3]. In Poland in 1996 bladder cancer was the fourth most frequent male cancer with 3070 new cases in men, accounting for 5,4% of all malignancies [4]. Mortality rates vary significantly among European countries, especially low survival figures have been noted in some eastern European countries. In Poland in 1996 the overall 5-year survival in men was about 43%. This huge difference in survival may be attributed partially to a lower socio-economic status of Polish inhabitants compared with EU citizens (an association between deprivation and survival has been found for cancer in the bladder [5]). Another

important factor responsible for this situation might be the low popularity of adjuvant treatment in superficial tumours and lack of strong cooperation between urologists and oncologists resulting in a small proportions of patients receiving radiotherapy or chemotherapy.

SUPERFICIAL BLADDER CANCER

Superficial bladder cancer (Ta, Tis, T1) accounts for 70% to 80% of all bladder tumours. The recurrence rates after initial treatment range from 50 to 80%, with progression to a muscle-invading tumour in 10-25% [6,7]. Therefore, the prevention of recurrence and progression of the disease are the primary aims of treatment. The standard treatment consists of cystoscopic electroresection of the tumour (TURB) and adjuvant intravesical therapy in patients with a high risk of recurrence. Tis lesions, T1, and Ta high-grade (G3) tumours are associated with a high risk of recurrence and require adjuvant therapy to lower the risk of progression of the disease.

Adjuvant therapy is based on Bacillus Calmette-Guerin (BCG) or cytotoxic agents intravesical instillations. In Poland intravesical BCG therapy is less popular than in other European countries. BCG vaccine applied intravesicaly promotes inflammatory reaction in the bladder. Both the non-specific mechanisms mediated by NK cells (*natural killer*) and specific immune responses mediated by specific CTL (*cytotoxic T lymphocytes*) are engaged in the elimination of tumour cells. BCG-therapy of superficial bladder cancer is so far the most efficient kind of cancer immunotherapy. The pros and cons of chemotherapy and BCG-therapy are summarised in table 1. BCG-therapy is more efficient than intravesical chemotherapy because it not only lowers the risk of local recurrence but also decreases the rate of progression to muscle invasive disease and improves survival [8,9]. The treatment options for BCG-refractory tumours are cystectomy, intravesical chemotherapy with traditional cytostatic drugs (therapy usually not efficient) or valrubicine. The use of “new agents” (IIIrd generation cytostatics) such as gemcitabine, taxanes or valrubicin attract attention of many investigators. Valrubicin given over a 6-week course has been shown to be effective in ablating a marker tumour (complete histological regression) deliberately left in the bladder after incomplete TURB in 18 out of 39 patients with a refractory superficial disease [10]. Gemcitabine is also a widely tested compound and currently many phase I/II clinical trials currently under way around the world (Germany, Spain, Netherlands, USA, UK, Sweden, Israel) looking at optimal way to use gemcitabine in the treatment of the superficial disease. Results from these trials can be expected in the near future. Other studies put to test the hypothesis of enhancing the immunostimulating effect of BCG therapy by introducing interferon-alfa2b or bropermine (interferon inducer). Salvage intravesical therapy with interferon-alpha2b plus a low dose BCG might be effective in patients with superficial bladder cancer in whom BCG alone has previously failed [11]. Another interesting investigational approach is the use of recombinant BCG strains that secrete cytokines such as GM-CSF, interferon gamma, IL-12 or IL-2 [12]. IL-12 has several biological properties that seem useful in the immune therapy for bladder cancer. The significant antitumour responses with IL-12 in preclinical animal models of bladder cancer are also promising [13].

The ability to genetically manipulate mycobacteria attracting attention because it makes it possible to enhance immunogenicity with lower doses and thus potentially prevent disseminated mycobacteriosis in the BCG-therapy in cancer patients [14]. Cell wall skeletons isolated from various bacteria have anticancer activity. Mycobacterial cell wall-DNA complexes (MCC) perform their action by induction cytokines and directly inducting apoptosis. The use of MCC for bladder and prostate cancer seems to be an interesting option [15]. Another interesting approach to immunotherapy is based on dendritic cells. Dendritic cells are able to present tumour antigens to T cells very efficiently. Recently has been shown that autologous dendritic cells pulsed with MAGE-3 (tumour antigen expressed

in melanoma and other tumours) peptide are able to induce reduction of lymph node and liver metastases in three out of four bladder cancer patients [16].

It is now possible to distinguish between different types of immune responses to BCG in cancer patients by examining cytokine profile in the urine. Interleukin-2 (IL-2) and interferon-gamma are released during T helper 1 lymphocyte responses, and IL-10 is released during T helper 2 lymphocyte responses. T helper 1 lymphocyte urinary cytokine profile is associated with a favourable prognosis after bacillus Calmette-Guerin (BCG) treatment. Urinary IL-2 levels may serve to identify patients at risk for bladder cancer recurrence after a single course of BCG and, thus, to tailor individual treatment [17,18]. The established prognostic factors such as grade, number and size of lesions, and resistance to BCG-therapy are too crude to precisely tailor therapy and follow-up policy to the individual patient who will frequently require cystectomy or radio/chemotherapy. Traditional diagnostic methods of local recurrence such as cystoscopy and cytological examination of the urine have limited sensitivity and specificity. The new methods of detecting tumour cells in urine are developed and tested mostly in small cohorts (dozens of patients), and the most promising of them deserve verification in the context of large randomized phase III trials. Another example of diagnostic tool is a microsatellite analysis DNA test in the urine which reliably signals the presence of recurrent bladder carcinoma, sometimes even before cystoscopic evidence of recurrence. This non-invasive diagnostic tool has a potential to replace cystoscopy in many cases [19].

Cytogenetic analysis has provided strong evidence that loss of a suppressor gene or genes on chromosome 9 are frequently involved in the genesis of bladder cancer. Mutations of the p53 tumour suppressor gene have been identified in 50% of high grade and advanced stage of bladder tumours, and are important in determining the clinical course of patients with superficial tumours and survival after neo-adjuvant chemotherapy [20,21]. Oncogenes of the *ras* gene family have been found in bladder cancer. A correlation has been shown exist between the expression of *ras* protein and high histological grade. In addition, an association between *c-myc* oncoprotein expression and recurrence or invasion in superficial tumours has been shown. Methylation of the *c-myc* oncogene may also correlate with stage and grade. Flow cytometry may be helpful method for staging and planning treatment of bladder cancer in some cases. There appears to be a strong correlation between DNA content or ploidy and the level of differentiation (tumour grade), depth of invasion (tumour stage), and response to chemotherapy. Flow cytometry results correlate with chromosomal changes. Progression and recurrence of tumours correlate with aneuploidy and an increase in the proliferative rate [22]. Aneuploidy may by detected in urine early, predicting recurrence [23].

MUSCLE–INVASIVE AND LOCALLY ADVANCED BLADDER CANCER

The diagnosis of muscle invasive tumour (T2) or locally advanced bladder cancer (T3 to T4a) involves poorer prognosis. Only about 50% to 75% of patients with T2 stage disease survive 5 years and the proportion of survivors decreases with more advanced stages of the disease.

The therapy strategies for muscle-invasive stage of the disease can be divided into bladder sparing and non-bladder sparing strategies. The first strategy of treatment is represented radical cystectomy, which is a standard treatment in muscle invasive tumours (T2) and T3a tumours. However, half of patients has micrometastases at the time of surgery. Recently, it has been shown that wide resection of the perivesical soft tissue and extended lymphadenectomy (to the bifurcation of aorta) provides the best chance for curing locally advanced bladder cancer [24,25]. Thorough pelvic lymphadenectomy is indicated in all patients at the time of radical cystectomy, particularly if there no clinical evidence of nodal metastases [26]. Systemic treatment, administered before surgery (neoadjuvant) or after cystectomy (adju-

vant) is still a matter of debate. A review of published randomised trials of adjuvant chemotherapy identified four trials with a total of only 278 patients [27]. In these trials the older standard chemotherapy regimens such as MVAC and CMV were used. However, the results appeared to show a significant difference in favour of adjuvant chemotherapy in three of them but serious methodological flows were reported in terms of sample size, early stopping rules, statistics and reporting results. Therefore the definitive value of adjuvant chemotherapy is still unclear and we are waiting to obtain results of the well-designed and well-conducted phase III trial.

Since gemcitabine with cisplatin has become a new standard regimen in metastatic bladder cancer, this two-drug combination started to be used also in treatment of early stages of bladder cancer. MSKCC [28] runs a phase III study comparing gemcitabine and cisplatin (reference arm) with gemcitabine and doxorubicin combination (experimental arm). One of the major objectives of the trial is to determine if p53 and bcl-2 protein expression are predictive factors for sur-vival of patients treated with these regimens.

For neoadjuvant therapy the situation is not evident as well because recently published two clinical phase III trials do not give the clear answer a question about the role of neoadjuvant chemotherapy. One of those is negative, the other positive, and the latter has been the subject of substantial criticism. In the larger EORTC-MRC trial 976 patients were assigned to three cycles of CMV chemotherapy (cisplatin, methotrexate, vinblastine) or no chemotherapy before radical local treatment (cystectomy or radiotherapy depending on the investigator's and patient's preference) [29]. 3-year survival advantage of 5,5% in favour of neoadjuvant chemotherapy (55,5% vs 50%) was not statistically significant (p=0.075) at the time of publication, however mature results presented at ASCO 2002 have shown statistically significant survival benefit. The projected 5-year survival rate with neoadjuvant CMV was 52%. Chemotherapy was associated with a 15% decrease in risk of death (HR=0,85 CI 0,71-1,02). In the exploratory subgroup analysis, greater effect of chemotherapy was observed in the G3 subgroup vs. (G1 and G2) and with the increasing GFR (glomerular filtration rate). In conclusion authors of the study stated that these results do not justify the recommendation of neoadjuvant chemotherapy as standard treatment. However, they stressed several points that weaken the negative conclusion. In this trial broad category of patients, from cT2 to cT4a stage, was included, 34% were staged T2, in whom the benefit of adjuvant therapy may be less easy to demonstrate. The administered chemotherapy might be suboptimal because it did not contain doxorubicin. On the contrary, in the second major trial, primarily run by SWOG, neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, cisplatin) followed by cystectomy was superior to cystectomy alone [30]. 15% gain in the 5-year overall survival (57% vs 42%, p=0,04) and nearly doubled median survival were observed (6,2 vs. 3,8 years). The third study from M.D. Anderson, addressed the issue of chemotherapy timing [31]. A total of 140 patients with locally advanced tumours (with lympho-vascular invasion on TUR or T3b-T4a) received two courses of MVAC followed by cystectomy and 3 cycles of adjuvant MVAC or were treated initially with cystectomy followed by 5 cycles of MVAC. There were no significant differences in outcome between two groups but impressively high survival results in this high risk cohort of patients (58% of patients remained disease free with median follow-up of 6,8 years) and better tolerability of neoadjuvant regimen supports the use of upfront chemotherapy in a high risk patients. The complete pathological remission after neoadjuvant chemotherapy appeared to be a strong positive prognostic factor for survival and this fact was confirmed by the results of both cited studies. The important issue is to show that expression of p53, bcl-2 and others proteins may be helpful in selecting patients for different neoadjuvant chemotherapy regimens because the expression pattern may be establish after initial endoscopic resection (biopsy) of the tumour tissue.

SPARING STRATEGIES OF TREATMENT FOR MUSCLE-INVASIVE BLADDER CANCER

Another open question that remains to be answered is the potential of organ-sparing therapy without cystectomy in locally advanced disease. In contrast to the USA and mostly of EU countries in Great Britain and Canada radiotherapy is a standard local treatment. The clinical efficacy of cystectomy and radical radiotherapy has never been compared in head to head randomised trial. The survival figures are better in cystectomy series but one should bear in mind that groups treated with surgery and radiotherapy usually differed substantially. Patients in poor general condition are more often treated with radiotherapy than with surgery. Generally radiation therapy is reserved for patients who are medically unfit or who refuse surgery. Radiotherapy for patients with T2 to T4 stage of disease gives the probability of rendering the bladder free of disease at 5 years in range from 35% to 45%, and overall survival from 23% to 40% [32]. In most cases, radiotherapy were delivered to a total dose of 55 to 65 Gy with daily dose of 2 Gy, but the optimal total dose and way of fractionation is under debate. Recently introduced, 3-D conformal radiotherapy (3D CRT) technologies enable to deliver required radiation dose to the target volume of tumour tissues with greater precision. It allows improving the therapeutic gain of radiotherapy due to better delineation of target and improved protection of organs at risk (OAR). Another option of bladder-sparing strategy is radiotherapy combined with chemotherapy (concurrent or sequential), which is studied in several trials ongoing in Europe and in the USA [28]. Proponents of organ sparing therapy argue that radiotherapy combined with chemotherapy leaves room for cystectomy in case of local failure or initial lack of response after radio/chemotherapy [33]. There are not sufficient published data, which can support the introduction of bladder preservation therapy based on TURB with following by concurrent radio-chemotherapy.

Partial cystectomy represents an option of sparing approach for small, low grade solitary tumour which is located away from the bladder neck and trigone, and for older patients who are not good candidates for total cystectomy. Since the rate of local recurrence is high after partial cystectomy (30% - 70%) this strategy is not generally accepted as a sole method of treatment and usually is combined with neoadjuvant chemotherapy [34]. However, no clinical data have demonstrated so far a survival benefit due to application of neoadjuvant chemotherapy.

METASTATIC DISEASE

Generally bladder cancer is a chemotherapy sensitive disease and multi-agent therapy is more effective. MVAC regimen, developed at MSKCC was considered as the treatment of choice for the last decade. Unfortunately, high response rates (70%) attained with MVAC chemotherapy were associated with very few long- term survivors (3-5% at 5-year follow-up) and with substantial toxicity. Toxic deaths occurred in 3% to 4% of patients, neutropenic fever and sepsis in 20% to 30%, severe mucositis in 10% to 20%. Van der Maase et al. published in 2000 results of the randomised trial comparing MVAC to GC (gemcitabine-cisplatin) combination, which established a new standard chemotherapy regimen [35]. 405 patients with stage T4b or with metastatic disease were randomised to GC (gemcitabine 1000 mg/m2, days 1,8 and 15; cisplatin 70mg/m2, day2) or standard MVAC. Overall survival, time to treatment failure, time to progressive disease and response rate were very similar in both arms but safety profile and tolerability of GC regimen was superior. The toxic deaths rate was 1% on the GC arm, 3% on the MVAC arm, the neutropenic fever rate was 2% in GC group, 14% in the MVAC group, neutropenic sepsis was observed in only 1% of patients treated with GC and in 12% of MVAC-treated patients, mucositis in 1% of GC and in 22% of MVAC patients. Seven of the eight deaths were related to complications of neutropenia and one to complication of mucositis. The authors concluded that GC chemotherapy is a sa-

fer alternative to MVAC and should be considered the standard of care for locally advanced and metastatic patients and the potential of GC regimen should be investigated in earlier stages of the disease.

Since toxicity of MVAC chemotherapy was largely due to complications of neutropenia colony stimulating factors (G-CSF, GM-CSF) support was used to ameliorate the unfavourable toxicity profile. Sternberg et al. made a step forward and compare intensified MVAC (i-MVAC) regimen with G-CSF support with a standard MVAC. Recently published results of this trial showed that the support of G-CSF enabled to deliver twice higher doses of cisplatin and doxorubicin, with less toxicity as compared to the treatment without G-CSF [36]. A statistically significant benefit was observed in progression-free survival and response rates but not in overall survival or time to progression.

Above mentioned data demonstrates that gemcitabine and cisplatin regimen has high efficacy together with good tolerability and can be used for wider spectrum of patients. On the other hand intensified MVAC regimen administered with G-CSF has acceptable toxicity, but outcome of the patients remain practically unchanged. With this respect it's questionable whether prescription of expensive growth factors with intensified MVAC is worthy, even for fit patients.

FUTURE STRATEGIES IN TREATMENT OF BLADDER CANCER

Preclinical cancer models have demonstrated that the delivery of p53 gene to tumour cells by viral or non-viral gene transfer methods resulted in enhanced sensitivity to cytotoxic drugs or radiotherapy. Recently a successful adenovirus-mediated p53 gene transfer to the bladder tumours in patients with muscle-invasive disease have been reported. Safe, practicable gene transfer (intravesical instillation), and biological activity of p53 shown in this study provide a strong rationale for future phase II and III studies in patients with superficial high-risk bladder cancer [37]. Since BCG is the most efficient in superficial disease we may expect that different modifications such as genetically altered BCG-strains, cytokine secreting bacteria or cell wall extracts will be studied in BCG-refractory superficial disease.

Progress in chemotherapy of bladder cancer can be made with both introducing new drug combinations and new schedules of sequential chemotherapy. New regimens active in bladder cancer tested in clinical trials contain gemcitabine and taxane with or without cisplatin or a new-class drug such as inhibitor of signal transduction via EGFR (epithelial growth factor receptor) such as trastuzumab or ZD 1839 [28]. The ongoing largest phase III study is conducted by several American and European co-operative groups together (trial co-ordinated by EORTC, planned accrual 610 patients during 3 years) is comparing GC regimen with GC plus paclitaxel. At the same time unfit patients with compromised renal function are enrolled onto the EORTC trial comparing gemcitabine plus carboplatin vs. carboplatin, methotrexate and vinblastine. New schedules are based on the Norton and Simon hypothesis of maximising individual drugs or combinations of agents devoid of overlapping toxicity. In MSKCC phase III trial is run in which patients are receiving doxorubicin and gemcitabine followed by paclitaxel and cisplatin vs. adjuvant cisplatin and gemcitabine in patients with resected tumour.

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