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Value of Current Chemotherapy and Surgery in Advanced and Metastatic Bladder Cancer

Key Words

Bladder cancer · Chemotherapy · Surgery

Abstract

The aim of the present paper was to review findings from the most relevant studies and to evaluate the value of current chemotherapy and surgery in advanced unresectable and metastatic bladder cancer. Studies were identified by searching the MEDLINE® and PubMed® databases up to 2011 using both medical subject heading (Mesh) and a free text strategy with the name of the known individual chemotherapeutic drug and the following key words: 'muscle-invasive bladder cancer', 'chemotherapeutics agents', and 'surgery in advanced bladder cancer'. At the end of our literature research we selected 141 articles complying with the aim of the review. The results showed that it has been many years since the MVAC (methotrexate, vinblastine, adriamycin, cisplatin) regimen was first developed. The use of cisplatin-based combination chemotherapy is associated with significant toxicity and produces long-term survival in only approximately 15–20% of patients. Gemcitabine + cisplatin represents the gold standard in the treatment of metastatic bladder cancer. In conclusion, the optimal approach in the management of advanced urothelial cancer continues to evolve. Further progress relies on the expansion of research into tumor biology and an understanding of the underlying molecular 'fingerprints' that can be used to enhance diagnostic and therapeutic strategies. Cisplatin-based therapy has had the best track record thus far.

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Introduction

Urothelial cancer of the urinary bladder, most commonly of the transitional cell type, accounted for an estimated 386,300 new cases and 150,200 deaths in 2008 worldwide [1]. It is the second most common malignancy of the genitourinary tract after prostate cancer. Men are more likely to be diagnosed than women and to subsequently succumb to the disease. The effect of gender, race, and age on the outcome of bladder cancer (BC) has not been fully delineated, although one study from the United Kingdom did report worse outcome in women based on routine registry data [2]. An article by Bassi et al. [3] confirmed that delays in diagnosis and initiation of therapy have adverse effects on stage and survival. The median age at diagnosis is 65 years with as many as 10% of patients >85 years of age. Studies in this group are essential to define the optimal approach to care because a substantial number of people with advanced BC are elderly or have other poor-risk features (characterized by visceral metastasis, poor performance status (PS), and >5%

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weight loss). Advanced unresectable (T4b) or metastatic BC has historically been a chemosensitive tumor. Currently, cisplatin-based combination chemotherapy is considered to be the standard therapy for this disease. Regimens such as MVAC (methotrexate, vinblastine, adriamycin, cisplatin), CMV (cisplatin, methotrexate, vinblastine) and GC (gemcitabine, cisplatin) have been employed with relative risks (RRs) reported in up to 70% [4–6]. Despite these high RRs, toxicity and survival outcomes remain suboptimal. For example, MVAC therapy results in a median survival time of approximately 13 months and is associated with severe toxicities including myelosuppression, nephrotoxicity, stomatitis, and emesis [7]. In addition, treatment-related death rates have been up to 3%. In an attempt to minimize these toxicities, studies are under way to determine which patients would best benefit from therapy [8–10]. The aim of this paper was to review the current role of conventional chemotherapy and surgery in advanced, locally unresectable, and metastatic BC.

Methods

The literature review was conducted by searching the MEDLINE® and PubMed® databases up to 2011. Studies were identified using both medical subject heading (Mesh) and a free text strategy with the name of the known individual chemotherapeutic drug and the following key words: 'muscle-invasive bladder cancer', 'chemotherapeutics agents', and 'surgery in advanced bladder cancer'. All phase I–III studies concerning advanced unresectable and/or metastatic BC were considered. At the end of our literature research we selected 141 articles complying with the aim of this review.

Results

Prognostic Factors

In recent years prognostic factors of outcome for patients with advanced or metastatic urothelial cancer and factors predictive of response have been identified. Pretreatment prognostic features are known to have an impact on individual patient outcome. With the MVAC regimen, factors predicting lower RRs, increased toxicity and poor overall survival (OS) are the presence of visceral metastases, the presence of abnormal levels of alkaline phosphatase and a low PS score [11]. The intergroup study by Loehrer et al. reported a median survival of 18.2 months for patients with a favorable combination of

prognostic features compared with only 4.4 months for patients with adverse prognostic factors [12]. With long-term follow-up, none of the patients with liver or bone metastases was alive at 6 years [13]. These data have been confirmed in a study in which 203 patients treated with MVAC at Memorial Sloan Kettering Cancer Center (MSKCC) were divided into three risk categories on the basis of their Karnofsky PS and the presence or absence of visceral metastases. Five-year survival rates were 33, 11 and 0% for patients with 0, 1 or 2 of these adverse features, respectively [14]. Similar results were obtained by the Spanish Oncology Genitourinary Group in a phase I/II study of 56 patients with advanced urothelial tumors treated with gemcitabine, cisplatin and paclitaxel (GCP). Factors associated with a poorer survival in a univariate analysis were ECOG PS >0, the presence of visceral metastasis and more than one site of malignant disease. In a multivariate model, PS (p = 0.044) and visceral disease (p = 0.008) were independently significant for decreased survival. Median survival times in the groups of patients with 0, 1 or 2 of these risk factors were 32.8, 17 and 9.6 months, respectively [15]. Long-term survival results of a randomized phase III trial of 405 patients treated with MVAC or GC showed that a Karnofsky PS of 70%, the presence of visceral metastasis, >3 metastatic sites, M1 stage and elevated alkaline phosphatase were the most important poor prognostic factors [16].

Another phase II trial of 56 patients treated with GCP showed almost identical median survival times for patients within the same risk categories treated with MVAC [15]. Lin et al. with a multivariate analysis evaluating 12 variables in 79 patients treated with two cisplatin- and 5-fluorouracil-based regimens found that a Karnofsky PS of <80%, the presence of visceral metastasis and elevated alkaline phosphatase were independently prognostic of poor survival. The presence of 0, 1 or 2 and 3 adverse factors was associated with a median survival of 81.8, 13.2 and 4.6 months, respectively, with respective 2-year OS rates of 79, 20 and 0% [17]. As phase II outcomes are susceptible to selection bias, understanding the impact of these prognostic features, especially PS and presence or absence of visceral metastasis, allows for a better interpretation of phase II trial results.

Besides the clinical prognostic factors mentioned above, attention has recently been drawn to the role of genetic and molecular factors in predicting the response to chemotherapy [18]. Cisplatin resistance appears to be mediated by the nucleotide excision repair system which removes bulky platinum DNA adducts. The excision repair cross-complementing 1 *(ERCC1)* gene plays a pivotal

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role in nucleotide excision repair, and an increase in protein expression of *ERCC1* is likely to cause the cisplatin resistance phenotype. Patients with completely resected non-small-cell lung cancer and *ERCC1*-negative tumors appeared to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with *ERCC1*-positive tumors did not [19]. Similarly, ribonucleotide reductase subunit M1 (RRM1) has been shown to be involved in gemcitabine metabolism and DNA repair after chemotherapy damage. A high level of mRNA expression of RRM1 is predictive of the resistance of non-small-cell lung cancer to gemcitabine and platinum [20]. In the only published data for urothelial cancer, Bellmunt et al. used a multivariate analysis to evaluate nine variables, including *ERCC* mRNA expression, in 57 patients treated in two different GCP trials [20]. An ECOG PS of 1 and high *ERCC* mRNA expression (defined as >7, with the median *ERCC1* mRNA expression relative to the housekeeping β-actin being 6.6, range 2.2–19.9) were independently prognostic of poor survival. The presence of the 0, 1 and 2 adverse factors was associated with median survivals of 26.4, 23.4 and 13.2 months, respectively [20].

Systemic Chemotherapy

MVAC

The development of cisplatin-based combination chemotherapy regimens for the treatment of patients with advanced and metastatic urothelial cancer was pre-eminent in the 1980s. MVAC, CMV, CM (cisplatin + methotrexate) and CISCA/CAP (cyclophosphamide + adriamycin + cisplatin) have been considered to be among the most active regimens [9, 10, 21].

It has been 15 years since the MVAC regimen was first developed at MSKCC [22]. In 121 cases with bidimensionally measurable disease, the overall response (OR) rate was 72%, and of these 36% obtained a complete response (CR). Long-term survival was achieved in patients who attained CR. Patients who achieved a CR to chemotherapy plus surgery had twice the survival of patients who had partial response (PR) alone [9]. OS for the whole group was 13.1 months. Chemotherapy was shown to be more effective against nodal disease than visceral metastases [8–10, 21, 22]. These data have been updated by the MSKCC group, who reported results in 203 patients treated with MVAC regimens. At a median follow-up of 47 months, 46 patients attained a CR with chemotherapy alone. The 5-year survival rate was 40%. In 30 patients who had a CR with chemotherapy plus surgery, 5-year

survival was 33% at a median follow-up of 37 months. Post-chemotherapy resection of viable tumor resulted in long-term survival in selected patients [23]. Of note, response to cisplatin-based therapy is usually rapid. Elderly patients >70 years old, particularly those with compromised PS, may be treated by reducing all doses of chemotherapy by 20–30% in order to evaluate their tolerance to therapy. Given these high RRs with MVAC, the Southeastern Cancer Study Group studied MVAC versus single agent cisplatin. In 246 evaluable patients, response was observed in 12% treated with cisplatin, compared with 39% treated with MVAC. 17 (13%) patients achieved CR with MVAC (p < 0.0001). The median duration of response was 4.3 months with cisplatin compared to 10 months with MVAC. Median survival for MVAC-treated patients was 12.5 months compared with 8.2 months for patients treated with DDP (p = 0.0002). The question of superiority of MVAC versus CISCA was evaluated at MD Anderson center. MVAC was found to be superior to CISCA: the median survival was 11.2 months after MVAC compared to 8.4 months with CISCA. The CR + PR rate was 65% with MVAC and 46% with CISCA (p < 0.05). Thus two prospective randomized trials have clearly proven the superiority of MVAC over single-agent chemotherapy. The median survival after MVAC in these two studies was approximately 1 year, similar to the median survival reported at MSKCC (13 months) [23]. Analysis of 203 patients treated with MVAC at MSKCC revealed two independent poor prognostic factors that were internally validated: visceral metastasis (bone, liver and lung) versus lymph node/soft tissue and Karnofsky PS <80 [14]. The percentage of patients belonging to the 0, 1 and 2 risk categories was 32, 45 and 23%, respectively. Patients with no risk factors had a median survival of 33 months and a 33% likelihood of 5-year survival. Patients with 1 risk factor had a median survival of approximately 13 months and an 11% likelihood of 5-year survival. The survival impact of Karnofsky PS <80 and visceral metastasis was nearly identical. The median survival of the patient cohort could vary from 9 to 26 months simply by altering the proportion of patients from different risk categories.

MVAC is not the only cisplatin-based regimen in use. In Europe, CM, CMV and MVEC (methotrexate + vinblastine + epirubicin + cisplatin) are also commonly used. Unfortunately the use of cisplatin-based combination chemotherapy is associated with significant toxicity and produces long-term survival in only approximately 15–20% of patients. The median survival duration is only 13 months and long-term survival is attained in approxi-

Table 1. Adjuvant chemotherapy following cystectomy

Reference (first author)	Year	Regimen	Patients with chemotherapy	Patients without chemotherapy	Results
Skinner [64]	1991	CAP	47	44	benefit, few patients received therapy
Stockle [65]	1992	MVAC	26	23	benefit, few patients, no treatment at relapse
Otto [66]	2001	MVEC	55	53	no benefit

mately 15% of patients with metastases in visceral sites and 30% of those with nodal disease. In one study, only 3.2% of patients with metastatic lesions treated with MVAC were alive and free of disease [14, 22, 23]. In a recent study [24] external beam radiation therapy was associated to the combined use of MVAC in 30 patients defined with locally advanced or metastatic BC to determine tolerability and efficacy. After one cycle of MVAC, patients received external beam radiation therapy with half a dose of MVAC treatment followed by two more cycles. A CR was achieved in 43% of cases (13/30) and a PR in 37% (11/30). The median overall and progression-free survival was 25.5 and 12.8 months, respectively; grade 3 and 4 neutropenia occurred in 83% of patients and in 1 case a hemorrhagic cystitis was observed. Anyway in this study, as in other radiotherapy studies, a heterogeneous sample of patients, with stage from T2 to T4, not only unresectable but also refusing radical cystectomy, was enrolled. We illustrate the main trials of chemotherapy for muscle-invasive BC in table 1.

Therefore other therapeutic options and strategies are clearly needed. Increasing the dose intensity of established chemotherapeutic regimens such as MVAC by adding hematopoietic growth factors may or may not lead to an improvement in OS. Novel chemotherapeutic agents, such as taxanes and gemcitabine, are among the most interesting therapeutic options available [8, 14, 24].

Gemcitabine and Taxanes

Gemcitabine is an antimetabolite that inhibits DNA synthesis and ribonucleotide reductase. Gemcitabine has been evaluated in a number of phase I/II trials [25]. Overall RRs have ranged from 23 to 29% and CRs have ranged from 4 to 13%, in both previously treated and untreated patients [26–30]. Toxicity, particularly myelosuppression, was mild and generally without grade 4 toxicities. Owing to moderate single agent activity of gemcitabine in frontline and salvage therapy, it has been combined with cisplatin to yield the GC regimen [27, 30–33]. A combined

mature analysis of three phase II trials totaling 121 patient revealed a median OS of 13.2 months and an estimated 4-year survival of 13% [34]. In a univariate analysis, the presence of visceral metastases and a hemoglobin level of <12.5 mg/dl had significant adverse prognostic implications. PS was not a significant predictor of survival, probably because only 14% of patients had an ECOG PS of 2. In a multivariate analysis only the absence of visceral metastases conferred a better prognosis, with an estimated 24% 4-year survival in such patients. A multicenter randomized trial was designed to detect a 33% improvement in survival with GC compared with MVAC [16, 35]. The trial accrued 405 patients and results revealed similar efficacy outcomes for GC and MVAC. The median survival (14 months for GC vs. 15.2 months for MVAC), the 5-year survival (13 vs. 15.3%), the RR (49 vs. 46%), the median progression-free survival (PFS) (7.7 vs. 8.3 months) and the 5-year PFS (9.8 vs. 11.3%) were all similar. The toxicity profile favored GC with a significant reduction in the incidence of grades 3 and 4 mucositis (1 vs. 22%), neutropenic fever (2 vs. 14%) and alopecia (11 vs. 55%). Severe emesis was similar for both regimens (21–22%). Although the overall median survivals were similar for both groups, the study was underpowered to detect equivalence in survival [16, 35]. However, given the significantly better toxicity profile for GC compared to MVAC and the superimposed survival curves over 5 years, GC has been recognized as an acceptable standard for metastatic transitional cell carcinoma. Analyzing all patients on the trial, those without visceral metastases had a median OS of 18.4 months and a 5-year survival of 20.9%, while patients with visceral metastases had a median survival of 10.3 months and a 5-year survival of 6.8%. Patients with a baseline Karnofsky PS of 70 had a median survival of 8.3 months, while patients with a Karnofsky PS of 80–100 had a median survival of 16 months [16, 35].

Recent retrospective data for neoadjuvant therapy with GC before cystectomy also suggest that GC is simi-

lar to MVAC in terms of pathologic complete remission rate [36]. In a phase I study a combination of radiochemotherapy was used in 33 patients with advanced unresectable bladder tumor: a dosage 75 mg/m² of gemcitabine once a week was given concurrently with standard radiotherapy of 60 Gy/6 weeks. Tolerability was found to be acceptable with a 3-year local PFS of 81% [37]. Trials attempting to combine GC with novel biologic compounds (bevacizumab, sorafenib, sunitinib and cetuximab) to improve outcomes are ongoing or already planned.

Paclitaxel (Taxol) and docetaxel (Taxotere) share a similar mechanism of action: the promotion of microtubule assembly and the inhibition of microtubule disassembly [38]. In previously untreated patients, single-agent paclitaxel, administered in a 24-hour infusion, produced an overall RR of 42% [39]. However, in patients with advanced transitional cell carcinoma of the bladder refractory to previous chemotherapy, single-agent paclitaxel induced a RR of only 7% [40]. Likewise, single-agent docetaxel as a first-line therapy produced RRs of 31% [41] and 45% in 11 patients with impaired renal function [42], while in patients previously treated with cisplatin-based chemotherapy a 13% RR was achieved [43]. Paclitaxel or docetaxel given in combination with cisplatin has displayed moderate activity, although cisplatin and docetaxel were inferior to MVAC in a randomized trial [44, 45]. Based on the activity of taxanes, they have been combined with GC to create triplet regimens [17, 46]. The GC-taxane triplets exhibited RRs of approximately 70% with median survivals of 15–16 months. Notably PS and visceral metastasis were independently prognostic with PCG (paclitaxel + cisplatin + gemcitabine) and were incorporated as the stratifying variables in the randomized clinical trial comparing PCG and GC. Median survivals in patients with 0, 1 or 2 of these risk factors were 32.8, 17 and 9.6 months, respectively.

The EORTC conducted a randomized phase III trial comparing GC with PCG and has recently reported early results. The trial objective was to detect an improvement in median survival from 14 to 18 months (hazard ratio: 0.78) with α = 0.05 and β = 0.2; 610 patients were deemed necessary [47]. Stratification factors were PS and metastatic versus nonmetastatic (locally advanced) disease and 627 patients were actually enrolled. The major risk groups were evenly distributed. The median survival (12.8 vs. 15.7 months; p = 0.1) and PFS (7.7 vs. 8.8 months; p = 0.109) were not statistically different for GC and PCG [48]. However, a subset analysis revealed an intriguing improvement in survival (p = 0.034) for patients with bladder primaries that comprised approximately 80% of all patients. However, this subset analysis hypothesis generating does not constitute high-level evidence and lacks the power to make firm conclusions. The overall RR was superior for PCG compared with GC (57 vs. 46%; p = 0.02). The trial further validated the MSKCC risk groups based on PS and visceral metastasis. As expected, PCG was more toxic with more neutropenic fevers (12.5 vs. 3.8%), diarrhea (18.9 vs. 8.9%) and alopecia (50.6 vs. 15.6%). However, thrombocytopenic hemorrhage was less common with PCG (6.8 vs. 11.4%) [49]. Therefore, PCG has not replaced GC as a standard. This study is being further analyzed and updated, and further presentations and publications are awaited. Potentially, the higher RR for PCG may be advantageous in the neoadjuvant setting to improve resectability and long-term outcomes; this hypothesis needs further study. Gemcitabine plus cisplatin still represents the gold standard in the treatment of metastatic BC.

Cisplatin-Refractory Bladder Cancer

Considering that patients recurrent after the standard cisplatin-based therapies have a poor prognosis, other second-line therapies not involving cisplatin are currently being studied. They concern principally the combination regimen of paclitaxel and gemcitabine (PG) as second-line therapy, as well the third-generation semi-synthetic vinca alkaloid vinflunine. Takahashi et al., in a phase II trial, showed an OR of about 30% in 20 platinum-refractory patients treated with an association of PG, obtaining a median survival of 11.5 months [49]. Almost the same results were obtained by other authors using a combination of PG: the OR rate varied from 30 to 33% and the survival from 11.3 to 12.1 months [49, 50].

Vinflunine exerts its anticancer activity by inducing a mitotic block mediated through the suppression of microtubule dynamics. In the first phase II study by Culine et al. [51], 51 cisplatin-resistant patients were treated with 320 mg/m² of vinflunine every 3 weeks. OR rate was 18%, while median PFS and OS were 3 and 6.6 months, respectively. Toxicity includes a rate of 67% of grade 3–4 neutropenia. Subsequently, Vaughn et al. [52] showed, still in a phase II study and with the same dosage, an OR rate of 15% among 151 patients. Median PFS and OS were 2.8 and 8.2 months, respectively; the adverse events were the same as in the previous study. In a phase III study 370 previously treated patients were randomized to receive vinflunine and best supportive care versus best supportive care only [52]. The intention-to-treat analysis showed a 9% objective responses and an OS of 6.9 months in respect of 4.6 months in best supportive care only, which

Table 2. Randomized phase III chemotherapy trials in advanced bladder cancer

Reference (first author)	Comparison	Patients	Overall response	Median survival, months
Troner [67]	cisplatin	48	16%	5.25
	cyclophosphamide + doxorubicin + cisplatin	43	21%	7.25
Saxman [13]	MVAC	202	46%	14.8
von der Maase [33]	cisplatin/gemcitabine	203	49%	13.8
McCaffrey [43]	MVAC	44	36%	15.4
	paclitaxel/carboplatin	41	28%	13.8

however was not statistically significant. On the other hand the adjusted multivariate analysis showed a statistically significant effect of vinflunine on OS with a 23% reduction in the risk of death. Toxicities included grade 3 and 4 neutropenia (50%), fatigue (19%), constipation (16%), and fever (6%); 1 toxic death occurred. An association of temsirolimus and vinflunine was tested in a patient with platinum-resistant metastatic BC obtaining a stable period of 3.8 months [53]. Some phase III randomized trials are summarized in table 2. Currently vinflunine has become the standard therapy in second-line treatment and should represent the comparator for further clinical trials in this setting [54].

The Role of Surgery in Advanced and Metastatic Bladder Cancer

Chemotherapy remains the treatment of choice for advanced and metastatic BC. Although metastatic BC is an aggressive neoplasm with rapid systemic dissemination, there is a subset of patients with regionally advanced disease who, following systemic chemotherapy, may benefit from 'adjuvant' surgical resection. This approach has been pioneered by a multidisciplinary group of investigators at MSKCC. Herr et al. have reported their experience with post-chemotherapy surgery in patients with locally advanced BC [55]. Throughout a 15-year period (from 1984 to 1999), 207 patients with either unresectable primary bladder tumors without obvious nodal involvement or inoperable, locally advanced bladder tumors with extensive pelvic or retroperitoneal nodal involvement received cisplatin-based multi-agent chemotherapy. 80 (39%) out of 207 patients underwent adjunctive surgical resection. In 24 patients no viable tumor was seen and 14 patients (58%) were alive at times ranging from 9 months

to 5 years. Residual viable cancer was completely resected in 49 patients (61%), yielding a complete clinical response to combined-modality therapy. A subset of 60 patients from the original group of 80 was treated with MVAC and was followed for more than 5 years. 19 of these patients had no residual tumor at resection and 9 (41%) were alive at 5 years. 34 patients were found to have viable tumor at resection. 5 of these had a CR, 27 a PR and 2 had no clinical response to chemotherapy before resection. Of the 34 patients who underwent surgery, 10 (29%) remained alive at 5-year follow-up, in contrast to 1 of 19 patients who either refused surgery or were technically unresectable [55].

Surgery may play a role when we are facing regional lymph node metastasis. The OS rate directly depends on the number of metastatic lymph nodes. Although in case of voluminous lymph node metastasis (N2–3) healing rates are low with surgery only, radical cystectomy and an extended lymph node dissection could be of benefit. Vieweg et al. have shown a significant correlation between disease-free survival and stage pN1, pN2 and pN3; 5-year survival rates were 44.2% in pN1, 26.6% in pN2 and 0% in pN3 patients already after 3 years of follow-up, respectively [56]. On the other hand, nodal stage was not an independent variable for survival and local recurrence rates in a multivariate analysis made by Herr et al. [55]. As Mills et al. [57] showed, the role of the node metastatic size must also be considered. They found a significant statistical inverse correlation between the diameter of the major lymph node metastasis and OS. Herr and Donat in a retrospective study in stage pN2 and pN3 patients, who had undergone radical cystectomy and lymph node dissection, found a 25% rate of CR, demonstrating that also a subset of patients with important lymph node involvement may benefit from an accurate nodal dissection: OS was 27 months in patients with primary organ-confined disease, significantly better than the 14 months in those with primary non-organ-con-

fined disease [58]. Anyway a benefit in survival from an extended lymph node dissection was seen also by Yafi et al. in patients with an aborted cystectomy due to unresectable BC [59]. These results substantiate the benefit of post-chemotherapy surgery in patients who achieve clinical CR to chemotherapy, especially if no tumor is found in the surgical specimen. Otherwise the role of surgery in distant lymph node involvement is questionable.

Although several combination regimens can induce a high CR and PR rate in patients with metastatic disease, reports of durable CR, especially in patients with hepatic or bone metastases, are anecdotal. Several studies suggest that post-chemotherapy surgery in patients with unresectable or metastatic BC may impact upon survival. In the original series of patients treated with MVAC at MSKCC, 11% of patients underwent post-chemotherapy resection of residual disease. Although this series included highly selected patients, many of the patients achieved long-term disease-free survival with this approach [9].

In another study [54], 31 patients with metastatic urothelial cancer underwent metastasectomy with the intent of rendering them free of disease. All gross disease was completely resected in 30 patients (97%). The most frequently resected location was lung in 24 cases (77%), followed by distant lymph nodes in 4 (13%), brain in 2 (7%) and a subcutaneous metastasis in 1 (3%). The 5-year survival from metastasectomy was 33%. Median time to progression following metastasectomy was 7 months. Five patients were alive and free of disease for more than 3 years after metastasectomy. The median survival from time of metastasectomy was 23 months. Similar results were reported in a German experience where 44 patients with metastatic BC who had complete resection of all metastatic sites were retrospectively reviewed. Metastasis included retroperitoneal lymph nodes (56.8%), distant lymph nodes (11.3%), lung (18.2%), bone (4.5%), adrenal gland (2.3%), brain (2.3%), small intestine (2.3%) and skin (2.3%). In 34 out of 44 patients, systemic chemotherapy and surgery were associated: 5-year OS was 28% with median overall, disease-specific and progression-free survival of 27, 34 and 15 months, respectively [60].

Sweeney [61] evaluated the role of retroperitoneal node dissection in patients with metastatic transitional cell carcinoma in retroperitoneal lymph nodes after a significant response to chemotherapy. In 10 patients, 4-year disease-specific and recurrence-free survival was 37.5 and 22.5%, respectively. The presence of tumor in two or fewer nodes correlated with greater disease-free and disease-specific OS. In a prospective phase II trial [62], 70 patients refractory to MVAC chemotherapy were treated with complete surgical resection of metastases. Patients with asymptomatic (n = 19) and symptomatic (n = 51) secondary cancer were included in the study. The median survival time was 7 months. Survival (1-year survival rate of 30% and 2-year survival rate of 19%) was found to be independent of the site of metastasis. However, 42 (83%) of 51 patients with symptomatic cancers did benefit from surgery in terms of tumor-related symptoms and performance score. Surgical removal of metastases from BC refractory to systemic therapy has an impact on quality of life in patients with symptomatic disease. Asymptomatic patients felt worse after surgery and no survival advantage was attained.

Abe et al. retrospectively reviewed 48 patients and noted significantly longer median OS in 12 patients who had undergone metastasectomy after systemic chemotherapy compared with those who had not undergone surgery (42 vs. 10 months; p = 0.0006) [63].

Anyway the presence of visceral metastasis is synonymous with a poor prognosis. However, some data suggest a beneficial role for surgical consolidation and visceral metastasectomy in a select group of patients, but those with multiple metastatic lesions within a visceral organ or more than one visceral site involved are unlikely to benefit from post-chemotherapy surgical resection.

Analysis of these small series permits only limited conclusions that must be confirmed in larger trials: (1) Only patients with a major response to chemotherapy in whom persistent disease is still evident may benefit from post-chemotherapy surgery. (2) Survival benefit is more evident for patients with unresectable primary or with metastatic regional lymph nodes. (3) Within the group of patients with more widely metastatic disease, only those patients with a solitary metastatic site either in lymph nodes or lung may benefit from adjuvant surgery. (4) Patients with persistent disease in multiple sites after chemotherapy or patients with disease in liver or bone do not appear to benefit from post-chemotherapy surgery.

Conclusions

The optimal approach to the management of advanced urothelial cancer continues to evolve. Further progress relies on the expansion of research into tumor biology and an understanding of the underlying molecular 'fingerprints' that can be used to enhance diagnostic and therapeutic strategies. In advanced unresectable and metastatic disease, cisplatin-based therapy (particularly MVAC and GC) has had the best track record thus far. As

a result, these regimens are recognized as the standard of care for metastatic and unresectable BC. Carboplatin-based therapy is, however, a viable therapeutic approach for patients who are poor candidates for cisplatin-based therapy. The decision who should receive which combination of agents seems to be largely determined by the individual's comorbidities, PS, and disease extent. While not statistically significant, the results of several phase III trials using MVAC and of phase II trials using carboplatin suggest a small benefit of cisplatin over carboplatin in median survival, which is balanced by the treatment-related toxicity [33]. Whether or not this implies that younger patients with aggressive and extensive disease should receive cisplatin regimens while elderly patients with a poor PS receive carboplatin-based treatment has not been definitely evaluated. Several studies suggest that surgery in patients with advanced BC may impact upon survival. Post-chemotherapy surgical resection of residual cancer may result in disease-free survival in some patients who would otherwise die of the disease. The best candidates for surgery are patients whose pre-chemotherapy sites of disease are restricted to the lymph nodes or to a single metastatic site other than liver and bone and who have had a major response to chemotherapy. Future improvements in the treatment of advanced BC will rely not only on the optimization of currently available cytotoxic agents, but also on the biologic profile of individual patient tumors and the appropriate therapies that target molecular aberrations unique to this malignancy.

Disclosure Statement

The authors have nothing to disclose.

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