Chemotherapy in the post-MVAC era: the case for adjuvant chemotherapy

Abstract  Radical cystectomy for muscle invasive and locally advanced bladder cancer is the standard treatment modality in most of the Western industrialised countries. Rates of perioperative mortality from radical cystectomy have decreased to less than 2% over the past two decades due to advances in surgical technique and perioperative care. However, at least 40% of patients with pT3 bladder cancer and 70% of patients with lymph node-positive disease develop tumour recurrence after radical treatment within the first 5 years when treated with radical cystectomy alone. After the efficacy of combination chemotherapy for metastatic urothelial cancer using methotrexate, vinblastine, adriamycin and cisplatin (MVAC) was first described in 1985, several cisplatin-based systemic regimens have been investigated as adjunctive treatment before or after therapy for locally advanced bladder cancer by radical surgery or radiation therapy. Three randomised studies have reported superior results of postoperative adjuvant systemic chemotherapy compared to radical cystectomy alone for locally advanced bladder cancer. All three studies demonstrated a significant survival benefit for bladder cancer patients receiving adjuvant combination therapy. Studies have been criticised for small patient numbers and statistical shortcomings. New effective antineoplastic agents, such as paclitaxel and gemcitabine, have evolved during the past decade as promising substances for the treatment of urothelial cancer. This article reviews adjuvant studies from the era of MVAC combination chemotherapy, as well as contemporary studies that discuss new antineoplastic agents for systemic adjuvant chemotherapy of locally advanced bladder cancer.

Keywords  Adjuvant chemotherapy · Locally advanced bladder cancer · MVAC · Radical cystectomy · Polychemotherapy

The incidence of invasive or high-grade bladder cancer in the United States in 1998 was estimated to be 18 new cases in a white population of 100,000 [20]. The mortality rate for invasive bladder cancer in 1998 from the “Surveillance, Epidemiology, and End Result (SEER)” database of the U.S. National Cancer Institute was estimated to be six men and two women per 100,000. The 5-year relative survival rate for patients diagnosed with muscle-invasive and locally advanced bladder cancer is around 50%. Even after treatment with radical surgery, less than 50% of patients with locally advanced bladder cancer will be without disease progression 5 years later. Locally advanced bladder cancer is defined as a muscle-invasive tumour growth beyond the bladder wall and/or involving regional lymph nodes, which includes pelvic lymph nodes below the aortic bifurcation (tumour stages pT3a, pT3b, pT4a and/or pN+, 1997 TNM classification [24]).

Adjuvant chemotherapy, administering antineoplastic agents after surgical removal or definite radiotherapy of a diseased organ, has been established for a number of tumour entities, such as breast, colorectal and lung cancer, leading to improved survival and progression-free intervals.

The first report stating urothelial cancer as notably responsive to combination chemotherapy was published in 1985 by Sternberg and colleagues [28]. This report introduced methotrexate, vinblastine, adriamycin and cisplatin (MVAC) combination chemotherapy to patients with metastatic transitional cell carcinoma, resulting in major clinical response in 17 of 24 patients (71%). This report also reported considerable toxicity with the MVAC regime, resulting in drug-related sepsis of four patients and one toxic death.

Subsequently, two randomised, phase III trials compared MVAC combination therapy to single-agent
cisplatin [10, 22] or to cisplatin, cyclophosphamide and adriamycin (CISCA) combination therapy [11] in advanced and metastatic disease. MVAC combination therapy succeeded as the “gold”-standard therapy for metastatic urothelial cancer since these trials demonstrated superior response rates (MVAC 65% vs CISCA 46%, MVAC 39% vs cisplatin 12%) and prolonged overall survival (median time MVAC 48.3 weeks vs CISCA 36.1 weeks and MVAC 12.5 months vs cisplatin 8.2 months).

Based on these results, MVAC and cisplatin-based combination chemotherapy was added as neo-adjuvant and adjuvant treatment options to definite therapy by radical cystectomy or radiation therapy in patients with locally advanced bladder cancer, including tumour stages pT3a–pT4a and/or pN +.

Initially, the neo-adjuvant approach has been favoured, documented by a dozen randomised, neo-adjuvant studies, in contrast to only five randomised, adjuvant studies for locally advanced bladder cancer during the past decade [7, 17, 21, 23, 30].

Only three reports of neo-adjuvant chemotherapy suggested a survival benefit [1, 14, 19]. In the first of these three studies, a 15% progression-free survival advantage calculated in a subset of patients with T3-T4a disease after neo-adjuvant chemotherapy with cisplatin and adriamycin did not lead to improved overall survival [14]. Later, this advantage in progression-free survival could not be reproduced in a successive study by the same investigator group using cisplatin and methotrexate [15]. The most recently reported study performed by a North American collaborative group demonstrated a survival benefit in 150 patients with locally advanced bladder cancer who received three courses of MVAC prior to radical cystectomy compared to 157 patients undergoing radical cystectomy alone [19]. Although median survival of 6.2 years for the neo-adjuvant chemotherapy group vs 3.8 years for the surgery only group clearly suggests a survival benefit for the neo-adjuvant group, the study has been criticised for a significant stratified log rank test result of $P=0.048$ calculated in a one-sided fashion instead of a non-significant two-sided log rank test ($P=0.08$) [27].

Since the majority of neo-adjuvant studies have not shown significant survival differences, most “published opinions” are currently not recommending neo-adjuvant chemotherapy for locally advanced bladder cancer as the standard concept. On the other hand, minor survival advantages and improved survival in subgroups, such as T3/T4a [14] or responding patients [3], have been described in a number of neo-adjuvant series, indicating that the neo-adjuvant concept will regain importance as soon as more efficacious schedules of chemotherapy are available. At present, however, the high rate of patients with non-responding tumours must be regarded as the main obstacle against successfully implementing the neoadjuvant strategy. In non-responding patients, neo-adjuvant treatment will not only not improve survival, but reduced survival must be expected because of the delay in performing cystectomy. A deteriorating prognosis in non-responding patients may, therefore, be the prominent reason for the disappointing results obtained in neo-adjuvant trials.

Consistent with this concept, it would be logical that minor improvements in the prognosis from neoadjuvant chemotherapy would translate into major improvements after adjuvant treatment regardless of the efficacy of combination chemotherapy. If neo-adjuvant treatment will ever convincingly be shown to be beneficial, the same effect, at least, can be expected after adjuvant treatment, but not vice versa.

**Adjuvant studies from the MVAC era**

A first retrospective analysis on adjuvant chemotherapy for locally advanced bladder cancer performed in a comparative, non-randomised design was published by Logothetis in 1988 [12]. High-risk patients with vascular invasion in the primary tumour, presence of nodal metastases, extravesical growth and/or direct invasion into pelvic viscera (prostate, vagina) were stratified for adjuvant treatment or surgery alone. Of 71 patients, 50 (70%) who were treated with five courses of adjuvant CISCA (cisplatin, cyclophosphamide, and adriamycin) combination therapy were disease-free at 5 years after radical cystectomy compared to 23 of 62 patients (37%) treated with cystectomy alone ($P=0.0001$).

Encouraged by these results, three randomised studies by Skinner [23], Stöckle [30] and Freiha [7] reported significantly delayed tumour progression and increased survival rates in patients randomised for adjuvant combination chemotherapy after radical cystectomy of locally advanced bladder cancer compared to patients without adjuvant treatment (Table 1). All three studies recruited patients with similar disease stages pT3–pT4a and/or regional lymph node involvement.

The first study by Skinner and co-workers of adjuvant combination chemotherapy in locally advanced transitional cell carcinoma of the bladder randomised 91 patients for cystectomy plus four cycles of adjuvant chemotherapy or radical cystectomy alone between 1980 and 1988. The majority of patients in the adjuvant treatment arm received CISCA combination therapy. The trial was stopped due to an interim analysis that demonstrated a significant disease-free survival advantage for the adjuvant treatment arm 5 years after cystectomy (adjuvant 51% vs surgery alone 34%, $P<0.011$) while overall survival was not significantly prolonged (adjuvant 44% vs surgery alone 39%, $P=0.099$). In a subgroup analysis of patients with only one positive lymph node, seven patients in the adjuvant treatment arm had a superior disease-free and overall survival compared to ten untreated patients. However, patients diagnosed with two or more tumour-positive lymph nodes did not benefit from adjuvant treatment in terms of survival, suggesting an unfavourable outcome independent of adjuvant treatment.