Review Article

Neoadjuvant Chemotherapy: A New Standard for Muscle Invasive Bladder Cancer?

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Abstract

Bladder cancer is the seventh most common cancer and the ninth most common cause of cancer deaths for men worldwide. Cystectomy with pelvic lymph nodes dissection is the standard local treatment of muscle invasive bladder cancer (MIBC) (T2–T4). In the last decade, the management of MIBC had become multidisciplinary involving peri–operative chemotherapy (neo– or adjuvant chemotherapy). Randomized trials and meta–analyses confirmed the survival benefit of neo–adjuvant chemotherapy before local treatment (surgery and/or radiotherapy). Consequently, this sequence should be considered as standard treatment of choice, for patients with good performance status (0–1) and good renal function. The benefit of adjuvant chemotherapy is not clear for patients treated with primary surgery.

Keywords: Bladder cancer, Chemotherapy, Neoadjuvant, Adjuvant

Introduction

Bladder cancer is the ninth most commonly diagnosed cancer in the world with more than 380,000 new case per year and more than 150,000 deaths per year in 2008. It is the fourth most common cancer in men and the eighth most common cancer in women in USA. It is the sixth most common cancer in Morocco and the most common cause of cancer death in men in Egypt. Smoking is the strongest risk factor of this disease. In Africa, especially in Egypt, chronic infection by ***Schistosoma haematobium*** was the most common etiology. Bladder cancers are called muscle invasive (pT2) when they infiltrate the bladder muscle. Standard treatment in this setting is radical cystectomy with pelvic lymphadenectomy. In the last decade, the management of muscle invasive bladder cancer (MIBC) had become multidisciplinary involving perioperative chemotherapy (neo– or adjuvant chemotherapy) [1–4].

Review

Since 1990, the MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen was considered as a standard treatment in first line metastatic setting. Two randomized phase III trials confirmed the superiority of MVAC to CISCA and CDDP, respectively, in terms of overall response rate and overall survival. The MVAC is effective, but particularly toxic. The main high grade 3–4 toxicities were febrile neutropenia, alopecia, vomiting, anorexia, and renal insufficiency. To improve the result of MVAC, the intensification of the same protocol as HD–MVAC (all drugs delivered in one day every 14 days), was investigated in a phase III EORTC trial including more than 250 patients. Although overall survival, the primary end–point of the study was identical in the two arms, the HD–MVAC improved complete response rate from 10% to 25%, and progression free survival from 8.5 months to 9.1 months (p=0.03). In addition, the systematic use of Granulocyte Colony–Stimulating Factors (GCS–F), made the HD–MVAC better tolerated. Gemcitabine and cisplatin regimen was tested in first line metastatic setting in a phase III randomized trial. It has an equivalent efficacy as compared to MVAC and has a better safety profile. In the first line setting, MVAC, HD–MVAC and gemcitabine–cisplatin were all considered as three standard chemotherapy first line treatments of metastatic urothelial bladder cancer [5–8].

Perioperative chemotherapy may be administered either before or after surgery. MIBC was a systemic disease. After radical surgery, half of the patients develop distant metastasis and die of the disease. The benefit obtained in ORR and particularly in CRR of chemotherapy in metastatic setting lead the investigators to assess the impact of peri–operative chemotherapy

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Organization	Year	Number of patients	Primary end point	Neo-adjuvant treatment	Radical treatments	Results
MRC/EORTC [11,12]	1999	976	Overall survival	CMV	Radiotherapy or cystectomy	OS benefit confirmed at 8-year (HR, 0.84; 95% CI, 0.72–0.99; p = 0.037)
SWOG (INT-0080) [10]	2001	317	Overall survival	MVAV	Radiotherapy or cystectomy	At 8.7 years, median OSl was 77 months vs. 46 months (p = 0.06) in favor of neoadjuvant chemotherapy

Table 1: Pivotal phase 3 trials investigating neoadjuvant chemotherapy plus surgery vs surgery in invasive bladder cancer

Abbreviations: CMV : cisplatin, methotrexate, and vinblastine ; **MVAC :** methotrexate, vinblastine, doxorubicin, and cisplatin; **OS** : overall survival

in the treatment of MIBC. Neoadjuvant chemotherapy had several advantages: the early treatment of micro–metastatic disease; the systemic treatment is better tolerated by allowing the preoperative administration of chemotherapy; the evaluation of chemo–sensitivity of tumor; and the down–staging, which facilitates surgery [(4).] In addition, response and mainly complete response to chemotherapy, have significantly improved overall survival according to a result of a recent meta–analysis [(9)]. The main inconvenience to neoadjuvant chemotherapy was the delayed radical treatment in progressive patients and the over–treatment with neoadjuvant chemotherapy in low risk patients (pT2N0M0).

The role of neoadjuvant chemotherapy was confirmed by two pivotal trials and three meta–analyses [(4)]. The first pivotal trial was conducted by the US intergroup, and included more than 300 patients having stages T2–T4a MIBC [(10)]. Patients were randomized to receive surgery alone or three cycles of neoadjuvant chemotherapy based on MVAC followed by radical treatment (surgery and/or radiotherapy). This trial showed that NAC improved significantly the pathologic complete response rate (pCR) from 15% to 38% (p=0.001). Indeed, neo–adjuvant chemotherapy increased median survival at 8.7 years median follow–up (77 months vs 46 months, p=0.06) and 5 years OS (57% vs. 43%, p = 0.06). Although, a 1/3 of patients developed high grade toxicity, no toxic death was noted and no negative impact on surgery or post–operative complications were noted [(10)].

The second pivotal trial was the EORTC intergroup trial including more than 970 patients having MIBC. Patients were randomized to receive radical treatment alone or neoadjuvant chemotherapy based on CMV (cisplatin, methotrexate, and vinblastine) followed by radical treatment (surgery and/or radiotherapy). NAC improved significantly time to progression at 3 years by 9% and 3–year overall survival by 5.5% (HR=0.85, 95%CI, 0.71–1.01). In addition, an increase in 10 years survival was confirmed at 8 years follow–up, from 30% to 36% (HR=0.84; 95 CI, 0.72–0.99, p = 0.37) (11,12). The results of the US INT and EORTC trials contrast with the negative results of 7 other trials. This may be due to the proven superiority of the chemotherapy regimen (MVAC and CMV) used in these two trials and to the non–optimal treatments used in the other trials.

To confirm the high impact of neo–adjuvant chemotherapy, a meta–analysis of the ABC group based on individual data of more than 3000 patients treated in 11 randomized trials was conducted. This meta–analysis demonstrated that neo–adjuvant chemotherapy with cisplatin reduced the risk of death by 14% with an absolute benefit in survival of 5% at 5 years (p=0.003). In addition, it confirms that NAC reduced the risk of relapse by 22% with an absolute benefit in PFS of 9% at 5 years [(13)]. However, the use of NAC remains poor. Only 13% of patients received NAC in USA in 2007[(14)]. The limited use of NAC is due in part to toxicities associated with poly–chemotherapy regimens used such as MVAC. As a consequence, many oncologists have turned to regimens such as gemcitabine and cisplatin and HD–MAVAC due to the similar efficacy and a more favorable safety profile in the metastatic setting. In a recent systematic literature review of 7 non–randomized trials and 164 patients, NAC with gemcitabine – cisplatin (GC) was investigated. The authors showed that pathological down–staging to pT0 occurred in 26% with neo–adjuvant GC [(15)]. In a recent phase 2 trial, HD–MVAC was also tested in neo–adjuvant setting in 39 patients. Pathologic response of pT1N0M0 was achieved in 49% with HD–MAVAC, and high grade 3 toxicities occurred in only 10% and no neutropenic fevers or treatment related death was noted. Indeed, one year PFS was better in pathologic responders (89% vs 67%) and radiologic responders (86% vs 62%) [(16)]. Based on these recent published data, we can conclude

that neoadjuvant chemotherapy should be considered as a standard treatment of MIBC. Different regimens can be used in neoadjuvant setting: MVAC, HD–MVAC and gemcitabine plus cisplatin. HD–MVAC and gemcitabine – cisplatin have a better safety profile than standard MVAC and can be considered as the preferred options [17,18].

No clear evidence defines the impact of adjuvant chemotherapy in the management of MIBC. Randomized trials evaluating adjuvant chemotherapy in MIBC have small size and do not clearly confirm the survival benefit of this sequence. The literature reports at least 6 randomized trial with contradictory results. A small meta–analysis of the ABC group based on individual data of approximately 500 patients treated in 6 randomized trials showed that adjuvant chemotherapy with cisplatin reduced the risk of death by 25% with an absolute benefit in survival of 9% at 3 years [19]. Consequently, adjuvant chemotherapy should not be considered as a standard treatment and can be considered as a treatment option in patient with pT3–pT4/pN+ MIBC [17].

Competing interests

The authors declare that they have no competing interests and received no external funding to prepare this study.

Abbreviations:

MIBC: Muscle invasive bladder cancer;
MVAC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin;
CISCA: Cisplatin, Cyclophosphamide, Doxorubicine;
EORTC: European Organization of Treatment of Cancer;
D–MVAC: intensified MVAC;
ORR: Overall response rate;
CRR: complete response rate;
NAC: Neoadjuvant chemotherapy;

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