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Commentary Open Access

The Endless Debate Concerning the Timing of Chemotherapy in Muscle Invasive Bladder Carcinoma: Before or After the Radical Cystectomy?

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Commentary

The management of muscle invasive bladder cancer (MIBC) remains a true challenge. The treatment cornerstone is the radical cystectomy, but there is a high potential for metastatic recurrence despite dealing with an apparently localized disease. Thus, there is a propensity for micro-metastasis once there is muscle invasion. The 5-year overall survival is around 50%. Moreover, these patients are usually elder heavy smoker, with many smoking related comorbidities on top of the diagnosed malignancy. They usually consult the urologists for lower urinary tract symptoms or most commonly gross hematuria.

Unfortunately, most of the surgeons are convinced that these patients should be operated as soon as they are diagnosed. Medical oncologists don't agree with this approach and recommend the administration of a neo-adjuvant chemotherapy (NAC) whenever the patients are eligible. The validated protocols were chemotherapies consisting of 4 cycles of cisplatinum based combination: dose dense MVAC protocol (Methotrexate, Vincristine, Adriamycin, Cisplatin) or GC protocol (Gemcitabine, Cisplatin). Eligible patients are those who are fit to receive cisplatin: creatinine clearance >60 mL/min, performance status <2, no heart failure, no neuropathy, no hearing problems [1]. If the administration of cisplatin is not possible, the patient must undergo radical cystectomy without NAC. So, in the real life, only a minority of the patients are eligible for cisplatinum based chemotherapy. There is a continuous debate Urologists-Medical Oncologists for NAC *vs* upfront radical cystectomy [2].

The arguments pro NAC are the following:

I. Gain in overall survival, demonstrated by a meta-analysis including 11 RCT: 3005 patients treated with cisplatin-based combination chemotherapy. There is a significant survival benefit (HR=0.86, 95% CI 0.77-0.95, p=0.003), with 14% reduction in risk of death and 5% absolute improvement in survival at 5 years, associated with a significant disease-free survival benefit (HR=0.78 95% CI 0.71-0.86, p<0.0001) and a 9% absolute improvement at 5 years [2].

II. Prospective assessment of the tumor's chemo-sensitivity.

III. Better tolerance and compliance before undergoing a radical cystectomy which is an aggressive surgery.

IV. It is better to deliver the chemotherapy pre-operatively instead of a post-operative adjuvant chemotherapy (AC), because we won't be able to control chemo-sensitivity. Nevertheless, 30% to 50% of patients who were candidates for NAC before operation, do not receive AC post-operatively. Moreover, there are no convincing data regarding the effectiveness of adjuvant chemotherapy. It was shown that it helps in delaying recurrence with a trend to improve survival knowing that most of the adjuvant trials were non-randomized comparisons with inadequate sample size in large part due to poor accrual. In addition, these trials suffered from selection bias. Consequently, the medical oncologist will only recommend the AC in case the patients were operated upfront, either because they weren't referred before or they were ineligible for cisplatin-based chemotherapy. Nonetheless, the AC also consists of cisplatin chemotherapy [3].

On the other hand, the urologists defend the upfront radical cystectomy with the following arguments:

a. Lack of adequate pathological staging.

b. Possible delay of the potentially curative cystectomy. However, NAC was not associated with higher surgical complication rates [2].

c. Lack of validated predictive biomarkers for response and risk of overtreatment.

d. The administration of AC allows a risk-adapted decision making with both pathologic and clinical factors [4-6].

In conclusion, it is well known that MIBC is a potentially metastatic disease even in the absence of clinically detectable metastases. The debate pro/con for pre/post-operative chemotherapy has one objective: the intent to eliminate the micro-metastatic disease with chemotherapy. Unfortunately, the population suffering from MIBC the patients than 70-years-old in (30% to 40%) of the cases with borderline renal function and performance status making them ineligible for cisplatin. So, researchers must validate another option for neo-adjuvant/adjuvant treatment rather than cytotoxic systemic therapies. In the era of immunotherapy (IT), the different malignancies are being classified according to their mutation burden and inflamed status. Urothelial bladder carcinoma is among the tumors with a high tumor mutational load, as it is majorly induced by smoking. After the imminent successful results of immunotherapy as frontline and second line in the metastatic disease, will it gain a place in the pre-operative neo-adjuvant setting especially when the patient can't receive a cisplatin-based chemotherapy? Beside the non-eligibility for cisplatin-based chemotherapy, should we further treat the patients who undergo radical cystectomy and remain with a post-operative muscle invasive urothelial carcinoma or node positive disease? This is the rationale from the trials testing a post-operative adjuvant immunotherapy. The Table 1 resumes the ongoing immunotherapy

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Trial	Agent	Timing of the treatment	PDL-1 selection	Standard arm	Primary endpoint	Sample size
PURE 01 NCT02736266	Pembrolizumab (phase II)	Neo-adjuvant	No	No standard arm	pCR	90
ABACUS NCT02662309	Atezolizumab (phase II)	Neo-adjuvant	No	No standard arm	pCR	69
IMvigor 010 NCT02450331	Atezolizumab (phase III)	Adjuvant	No	Observation	DFS	700
Check Mate 274 NCT02632409	Nivolumab (phase III)	Adjuvant	No	Placebo	DFS	640
Ambassador NCT03244384	Pembrolizumab (phase III)	Adjuvant	No	Observation	DFS, OS	739
PDL-1: Program Death Ligand 1; DFS: Disease Free Survival; OS: Overall Survival; pCR: pathologic Complete Response						

Table 1: The different ongoing trials of immunotherapy in the neo-adjuvant or adjuvant settings for early muscle invasive bladder carcinoma.

trials in early, muscle invasive, non-metastatic bladder carcinoma. In the neo-adjuvant setting, the trials are testing if the immunotherapy will replace the chemotherapy when the patients are not eligible to receive this latter. However, the trials using IT in the post-operative setting are evaluating its indication either after a cisplatin based NAC and a resulting post-operative stage of ypT3, ypT4 and/or pN+, or when the patients undergo an upfront radical cystectomy without a NAC, and then they have an indication for adjuvant treatment outside the standard of care. In the last American Society of Clinical Oncology meeting (ASCO) 2018 meeting, T Powles presented the interim results of the ABACUS trial, a phase II trial testing the administration of neo-adjuvant Atezolizumab (Table 1), showing a pathologic Complete Response (pCR) of 40% in PDL1 positive sub-group versus 16% in the PDL1 negative subgroup [7]. In the same perspective, Necchi A presented the interim analysis of the PURE-01 trial consisting of a neo-adjuvant administration of Pembrolizumab (Table 1). She reported consistent results with 39.5% of pCR in the whole population group, irrespective of PDL1 [8]. The coming years are so promising, and the results of the trials presented in Table 1 are awaited. Additionally, further trials are adopting a combination of chemo-immunotherapy in the experimental arm. Finally, the personalized medicine is showing very interesting results. So, will we consider the genomic/molecular classification of transitional cell carcinoma of the bladder, and thus select the chemo-sensitive/resistant patients, without exposing them to treatment toxicities.

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