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Short Communication Open Access

Development of Management Algorithm for Non-Metastatic Muscle-Invasive Urothelial Cancer: A Short Communication by the Hellenic Genito-Urinary Cancer Group (HGUCG)

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Introduction

Urothelial cancer (UC) may develop anywhere along the urinary tract (kidney, ureter, bladder, urethra). It is characterized as non-muscle invasive, muscle invasive and metastatic, and these categories differ in prognosis and management. Non-metastatic UC is an ideal example for multidisciplinary management, since its treatment requires participation of urologists, pathologists, medical oncologists and radiation oncologists. Therefore, constant efforts of different medical societies to compose clinical practice guidelines (CPGs) on the management of non-metastatic muscle invasive UC (nmMIUC) have taken place [1-12]. The main issue is that most of these guidelines are based on different levels of evidence (LoE) producing different grades of recommendation (GoR) and, along with the lack of large randomised clinical trials, makes their implementation on everyday clinical practice problematic in certain aspects.

The Hellenic GU Cancer Group (HGUCG) performed a systematic review of published CPGs and produced a statement of practice, easy to apply and to be prospectively evaluated [13]. Development of guidelines de novo was not our purpose. We insisted more on a systematic review of the existing CPGs and their critical evaluation. Since radical cystectomy with bilateral pelvic lymph node dissection remains the undisputed standard of care, we focused on guidelines regarding non-surgical therapies used in association with or instead of definitive surgery [14].

We strongly recommend that stratification according to medical fitness or consent to undergo radical cystectomy, should be the first step upon diagnosis. Therefore in the cystectomy candidate group, neoadjuvant, adjuvant or perioperative chemotherapy were the options studied. And in the cystectomy non-candidate group, chemotherapy, radiotherapy or chemo-radiotherapy were studied.

Patients fit and willing to undergo cystectomy

In the fit and willing to undergo cystectomy group, neoadjuvant chemotherapy consisting of a cisplatin based combination has shown a 5-9% absolute survival benefit when added to radical cystectomy. MVAC and CMV are the two most used regiments and Gemcitabine/Cisplatin (GC) combination has shown greater acceptance during last years. Fitness for cisplatin should be based on the following criteria: ECOG PS <2, creatinine clearance >60 mL/min, hearing loss grade <2, neuropathy grade <2, and/or heart failure New York Heart Association Class <III [15].

Adjuvant chemotherapy is supported by data of lower level of evidence compared to the neoadjuvant approach, although it is still considered a standard of care in patients with high risk for relapse (pT3, pT4a, pN+) who have not undergone neoadjuvant chemotherapy. Cisplatin based combination remain the regimen of choice in this context too (Figure 1).

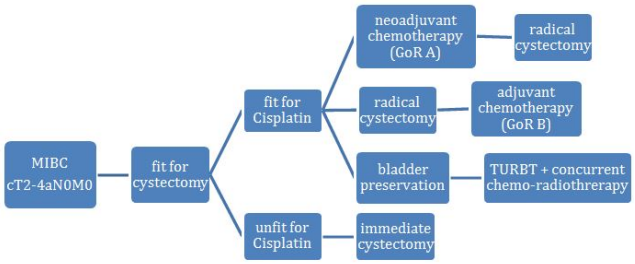

Figure 1: Proposed algorithm for fit for cystectomy MIBC.

Patients medically fit but unwilling to undergo cystectomy

In the small but really important group of patients who are medically fit but unwilling to undergo cystectomy, bladder-preservation protocol can be implemented. Traditionally, they consist of the trimodality approach: maximal trans-urethral resection of bladder tumor (TURBT) and external-beam radiation therapy with concurrent chemotherapy, followed by cystoscopic assessment of response with immediate cystectomy for nonresponders, and also active cystoscopic surveillance with salvage cystectomy at the first evidence of invasive recurrence. If such strategies are strictly followed, long-term outcomes appear similar to those of cystectomy series, although a direct comparison of the two approaches has not been performed. Bladder preservation option should be offered to patients with small tumours (<3 cm in diameter), no carcinoma in situ, microscopically complete TURBT and no hydronephrosis. Optimal radiosensitizer has not been clarified yet. Nevertheless, cisplatin remains the standard chemotherapeutic agent in this setting, and unfitness for cisplatin should exclude bladder preservation and lead to immediate cystectomy.

Patiens unfit for cystectomy

Unfitness for surgery is frequently associated with comorbidities which are also relevant for alternative therapies (i.e. optimal chemoradiotherapy or cisplatin-based chemotherapy). Taking into

consideration the usual population of urothelial cancer, the proportion of these "unfit" patients is apparently sizeable. "Optimal" management is inevitably individualized according to the feasibility of the available therapeutic options. Theoretically, tri-modality therapy remains the best approach, although unfitness for radical surgery may co-exist with unfitness for optimal chemotherapy or radiotherapy.

For patients who are unfit for surgery but otherwise fit for cisplatin and optimal radiotherapy, management should not differ from their fit-for-surgery counterparts who elect for bladder preservation. Radiotherapy alone has been traditionally used in the unfit for cisplatin group but novel encouraging data using radiosensitivity with 5-FU+Mitomycin C in this group have emerged.

The group of the elderly of unfit for optimal chemo-radiation represents a great challenge for multidisciplinary approach. Monotherapy as well as radiation hypofractionation or different schedules remain valid options, although the outcomes are poor compared to their fit counterparts Figure 2.

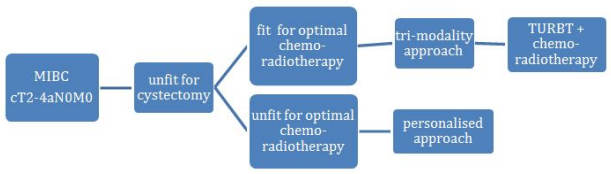

Figure 2: Proposed algorithm in the unfit for cystectomy MIBC.

Discussion

Urothelial cancer is an excellent example of multidisciplinary approach, which is imperative for obtaining the best possible therapeutic outcomes. Our effort to review the most important existing guidelines strongly emphasizes this cooperation. We would like to strongly stress the need for more clinical research in the field of unfit patients not only because this definition has not been clarified yet but also because "unfit" cancer patients are going to become a great percentage of our everyday practice in the years to come. Currently these patients are severely underrepresented in clinical trials, but aging of the population and advanced medical diagnostics will lead to a greater importance of this "unfit" population.

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