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Review

Unmet clinical questions in elderly patients with locally advanced and metastatic bladder cancer

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Bladder cancer (BC) is a deadly disease with high prevalence in elderly population. Several therapeutic issues are still unsolved in the clinical management of these patients. Radical surgery with or without perioperative chemotherapy represents the best therapeutic strategy in early-stage disease even though recurrence rates are high and few therapy options are available for recurrent patients. Platin-based chemotherapy is currently the standard of care for advanced disease with a poor life expectancy of about 12 months. Novel therapeutic options, including molecular-targeted agents and immunotherapy, are under preclinical and clinical evaluation with promising results.

A major issue in BC care is the management of elderly patients, a population with relevant co-morbidities, increased risk of life-threatening toxicities and currently not receiving the best therapy options. This review summarizes literature data about treatment strategies in elderly BC patients and the relevance of geriatric assessment to categorize fit patients who can receive standard therapies from unfit patients who should be treated with extreme caution.

Key words: Bladder Cancer, Chemotherapy, Elderly patients

INTRODUCTION

Bladder cancer (BC) is the 5th most common worldwide cancer. Risk factors include smoking, family history, prior radiation therapy, frequent bladder infections, and exposure to certain chemicals [1-3]. It is an age-associated malignancy, with the median age at diagnosis of 73 years. Individuals aged 75-84 years represent the largest percentage (30%) of new cases [3-5]. Data collected by the National Cancer Institute (Surveillance, Epidemiology, and End Results [SEER] Program), the Centers for Disease Control and Prevention (National Program of Cancer Registries) and the North American Association of Central Cancer Registries predicted 76,960 new urinary BC cases in 2016 with an estimated 18,000 deaths in the United States only [6]. In addition, the strong increase of elderly population is going to be a challenge for health care systems in the developed countries within few years, especially for cancer care. Therefore, BC care in elderly patients could be a real problem in daily practice [7] and, in such a context, different approaches are under evaluation for the BC management in elderly.

Curative therapy consists in either radical cystectomy (RC), with or without perioperative chemotherapy, or combined-modality therapy (CMT) having the goal of bladder preservation through a combination of maximal transurethral resection of bladder tumor, radiation therapy (RT), and concurrent chemotherapy [4]. The long-term survival depends upon the stage at diagnosis. The risk

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of recurrence estimated by a post-RC nomogram ranges from 20% for patients with organ-confined disease to 70% for those with limited lymph node involvement [8]. Conversely, metastatic disease remains incurable with current therapies, with a poor life expectancy of 14 months in patients who receive systemic treatments and 8 months without treatments [9,10]. A major issue in the daily medical practice is the lack of reliable tools for risk assessment in the elderly population. Therefore, curative (but risky) treatments are given only to a small percentage of elderly patients. Noon et al. addressed this issue by examining the records of 3,300 BC patients diagnosed in Sheffield, United Kingdom, between 1994 and 2009. They observed that, while more than half of patients under the age of 60 usually receives a potentially curative treatment (surgery or radiotherapy), the same happens only in one third of patients aged 70-79 and in 12% of patients over 80. Moreover, patients over 70 are more likely to die of BC and have a higher rate of more aggressive tumors. The conclusion is that elderly patients are currently not receiving the best treatment options [11]. While no treatment options are directly ruled out by chronologic age, age-related issues can impact on performance status and medical comorbidities, increasing significantly the risk of treatment-related toxicities and must be considered into decisions in order to optimally deliver patient oriented care. On the other hand, no curative treatment is to be spared in elderly patients only because of the age, if age related issues are minimal. This review summarizes the relevant literature regarding management of chemotherapy for Muscle Invasive Bladder Cancer (MIBC) and metastatic BC in the elderly population. Moreover, it discusses clinically available tools to guide management decisions in the elderly, specifically the comprehensive geriatric assessment (GA).

DEFINITION OF ELDERLY PATIENT IN BLADDER CANCER CARE

The definition of who can be considered elderly is a major issue in geriatrics. Previously, patients who were ≥ 65 years were generally considered to be part of this population, but this limit is constantly rising [12].

Classically, the term 'elderly' refers to advanced chronological age, but nowadays there are more relevant factors determining treatment decisions for this cohort of patients. For example, functional status and associated comorbidities of the individual patient are by far more significant than age. The actual trend is to classify elderly patients in "fit" (who are successful ager) and "frail". Fit patients, regardless of age, should be considered for aggressive interventions for BC, while frail patients may not benefit. The definition of a decision tool that allows a correct distinction between the two groups is an actual challenge. Fit patients have no significant functional impairments and/or comorbidities and, thus, should receive the best possible care options as often as possible. On the other end of the spectrum, frail patients demonstrate dependence in daily activities, significantly impaired mobility, relevant comorbidities, and/or at least one significant geriatric syndrome. These patients are at high risk for toxicities from cancer treatments. Decisional issues become even more complicated if we consider patients who are vulnerable and have concomitant mild functional or cognitive impairments, well controlled and nonlife threatening comorbid conditions, and/or depression. Depression in particular is often underestimated in the elderly population, probably due to its smoldering presentation. However, if a cut-off is needed, it is worth noting that most studies nowadays use 75 years of age to define elderly patients [12]. This population has been associated with many comorbidities and a shorter life expectancy [4,13]. However, it is important to remember that comorbiditities and age have been found to be independent predictors of overall survival (OS) in BC patients [14-16].

CHEMOTHERAPY FOR BLADDER CANCER IN ELDERLY PATIENTS

Neoadjuvant therapy

Studies have proven that cisplatin-based neoadjuvant chemotherapy (NAC) improves OS in patients with MIBC by approximately 5% at 5 years compared to radical surgery alone [17]. Furthermore, NAC doubles the rate of pathologic complete remissions at the time of surgery from 10-15 to 30% and improves 5-year OS approximately to 85% [18]. Therefore, based on the proven benefit and the level of evidence, NAC is the preferred approach to management for patients with MIBC who are eligible to receive cisplatin-based chemotherapy [19]. However, in clinical practice the use of cisplatin-based NAC is limited in both the community and academic centers [20] and this is mostly due to a misperception of the potential benefit by both physicians and patients and to the risk of increased toxicity. Thus, a coordinated multidisciplinary approach for patient's management has been proposed to increase the daily use of NAC [21,22]. This issue is even more relevant in the elderly population due to the higher risk of age-related toxicities. Thus, the incorporation of geriatric oncologists or skilled geriatricians in the administration and interpretation of the comprehensive geriatric assessment may

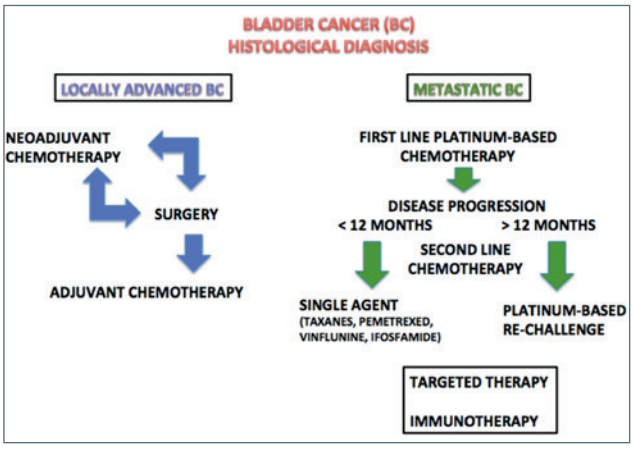

Figure 1. Available options in elderly patients with locally advanced and metastatic bladder cancer.

help to prospectively identify patients at increased risk for chemotherapy-induced toxicity [23].

In current literature, cisplatin is the cytotoxic agent with higher activity in the treatment of BC. However, in elderly patients, carboplatin is often used instead of cisplatin as first-line therapy because it is commonly perceived to have reduced toxicity in the elderly [24]. However, it is important to note that this alternative approach has not the same efficacy, since, in the neoadjuvant setting, carboplatin showed a reduced response rate. Thus, cisplatin-based chemotherapy should be considered in fit elderly patients when upfront cytoreduction is needed to improve the chance of curative surgery [24-26]. Conversely, a fraction of elderly patients is ineligible for cisplatin. An expert panel developed a tool for determine cisplatin ineligibility for the purposes of clinical trial development. However, these criteria fit perfectly in clinical practice and could be a reproducible standard for determining which patients are unfit for cisplatin [27]. While factors like poor performance status, high NYHA classes, low Creatinine clearance or peripheral neuropathy can preclude the use of cisplatin, age alone does not appear to affect tolerability or disease outcomes based on available data. Indeed, Chau et al. reported similar rates of eligibility for definitive local therapy following cisplatin-based NAC and similar clinical outcomes in patients aged ≥ 70 years versus younger patients with MIBC (pathologic CR, overall survival, and relapse-free survival at 3 years) [28].

In conclusion, cisplatin-based chemotherapy is an appropriate neoadjuvant strategy for elderly patients who are surgical candidates and have no contraindications. Patients who are ineligible for cisplatin, but are acceptable surgical candidates should be considered for surgery alone without chemotherapy.

Inoperable elderly patients, that have organ-confined disease and could tolerate cisplatin, can be treated with cisplatin-based regimens alone or in combination with radiotherapy. Alternatively, for those who are unfit for cisplatin, the best treatment option is a regimen based on gemcitabine, mitomycin C or fluoropirimidines [29].

Adjuvant therapy

Adjuvant chemotherapy is widely used in clinical practice for the management of MIBC, but a consensus has still to be established on which regimen is the most effective for improving postoperative survival. A systematic review and meta-analysis of clinical trials carried on by Hyung et al. found out that the only adjuvant regimen associated with an improvement in both the progression-free (Hazard ratio, 0.38; 95% Credible Interval, 0.25-0.58) and overall survival (Hazard ratio, 0.38; 95% Credible interval 0.22-0.65) is the gemcitabine/cisplatin/paclitaxel (GCP) combination [30]. This beneficial effect can be seen among all age groups. However, even if clinical improvements due to the adjuvant chemotherapy are clear, this regimen is underused in the elderly population in common practice. Leveridge et al. showed that the rate of administration of adjuvant chemotherapy is significantly lower in patients over the age of 70 (and almost non-existent in patient aged more than 80). Moreover, patients over 70 years receive a cisplatin regimen less frequently than younger patients and this is likely due to the common fear for co-morbidities in this category of patients. However, it is important to note that this choice can negatively impact on the prognosis of elderly fit patients. Hereby, the necessity for a tool that allows the selection between fit and unfit patients is a major clinical need, so that each group could receive the most appropriate therapy [4 13].

In this scenario, the criteria suggested for neoadjuvant therapy by Galsky et al. could be a reliable tool for decision-making [27].

METASTATIC DISEASE

First line therapy

Guidelines for the management of metastatic BC strongly recommend cisplatin-based combination chemotherapy as best option in first-line systemic therapy [31]. Recently, Galsky et al. published a meta-analysis about the tolerability and efficacy of cisplatin-based combination chemotherapy in metastatic disease based on data from eight Phase II and III clinical trials with a total of 543 patients. Surprisingly, no significant differences in the frequency of renal failure (grade 3-4), febrile neutropenia, or treatment-related death or median survival (12.1 months *vs* 12.8 months; p = 0.91)

were found in patients older and younger than 70 years of age [32].

Several studies were carried on in order to understand the best combination therapy in terms of risks and benefits for advanced BCs. The combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) was compared with the doublet of gemcitabine and cisplatin (GC) in a randomized Phase III study, showing comparable outcomes (median OS 15.2 *vs* 14 months, respectively). Noteworthy, the MVAC regimen was associated to increased rates of febrile neutropenia (14 *vs* 2%), grade 3/4 mucositis (22 *vs* 1%), and toxic death (3 *vs* 1%), whereas patients receiving GC reported improved performance status while on therapy, although differences between treatment arms were not statistically significant [31]. Therefore, GC is preferred over MVAC as first-line therapy for metastatic disease in the elderly, because of its best tolerance profile. However, as said before, some elderly patients are unfit for a cisplatin regimen and can be treated with carboplatin instead of cisplatin. Consistently with results of GC versus MVAC, gemcitabine/carboplatin produced similar OS rates as methotrexate/carboplatin/vinblastine (9.3 months *vs* 8.1 months) and decreased toxicity in cisplatin-ineligible patients with metastatic BC [33].

Second line therapy

Currently, the second line treatment following the use of a platinum agent is a complex issue. Indeed, we lack of a consensus about what regimen can be the most suitable in terms of PFS and OS. In such a scenario, several studies tried to address the question about the best treatment for a metastatic patient who underwent disease progression after a cisplatin-based chemotherapy. If the progression is observed later than 12 months after the end of first-line therapy, platinum re-challenge may be considered. Obviously, the choice between carboplatin and cisplatin in the elderly needs to be consider based on the patient's fitness. On the other hand, for patients progressing earlier than 12 months, single-agent chemotherapy, i.e., taxanes, pemetrexed, vinflunine and ifosfamide, was shown to be active and may be considered in patients eligible for additional therapy [34-38]. It should be considered that, recently, celecoxib was found to be able to enhance the effectiveness of certain chemotherapy drugs, *in vitro*. However, further studies are needed before clinical application of these findings [39 40].

Unfit patients (especially those with low performance status) should be treated with single agents in order to avoid toxicities, even if combination therapy could perform better. Nonetheless, the decision to proceed with any systemic therapy rather than with best supportive care alone under these conditions must be considered.

For both first and second line therapies, toxicities are an important limiting factor. Extremely helpful could be a study by Hurria et al. who identified prospectively risk factors associated with increased chemotherapy toxicity in the elderly. While age ≥ 72 years was *per se* a risk factor for toxicities, by far more important were low hemoglobin, low creatinine clearance and hearing impairment. Thus, based on this evidence, polychemotherapy instead of a single agent chemotherapy should also be avoided [23].

Considering the low clinical activity of second-line agents, participation in clinical trials should be strongly encouraged for all eligible patients with BC. There is awareness in the BC research community of the need for effective and tolerable therapies for elderly patients with BC and the importance of designing trials that do not exclude this vulnerable population [41].

Targeted therapies and immunotherapy

A new hope for the treatment of advanced BC may come from recent findings. Indeed, the advancement in the field of genetic and biology allowed a better molecular understanding of BC and showed the genetic heterogeneity of this disease and the existence of subtypes that may have treatment implications [42-55].

Even though the vast majority of patients with BC cannot benefit from targeted therapies, some reports showed dramatic and prolonged responses with the mammalian target of rapamycin inhibitor, everolimus, in metastatic BC [56 57]. In addition, immunotherapy with immune checkpoint blockade of programmed-death ligand 1 (PD-L1) represents a therapeutic option for elderly BC patients since these agents are highly tolerable and lack of significant toxicity [58].

The introduction of immune checkpoint inhibitors offers real hope for patients previously unlikely to achieve a durable response, including those who are unfit for platin. The improved tolerability of immunotherapy over chemotherapy directly correlates with its targeted mechanism of action. Currently, research is ongoing to further categorize responses and define ideal patient populations. Moreover, research is engaged in evaluating novel checkpoint inhibitors even beyond PD-1/PD-L1 plus CTLA-4, as indoleamine 2,3-dioxygenase (IDO) inhibitors, lymphocyte activation gene 3 (LAG-3), 4-1BB (CD137), T-cell immunoglobulin and mucin-domain-containing-3 (TIM-3), colony-stimulating factor 1 (CSF-1), tumor necrosis factor receptor superfamily, member 4 (OX40), and others, to address multiple pathways in immune system functioning. Thus, there is no doubt that immunotherapy will change the standard of care of BC [59].

CONCLUSIONS

It is widely accepted that elderly patients with BC represent a true challenge in decision-making [60]. Many comorbidities and hidden health problems can be found in a great part of them, especially those with a smoking history. All these factors can reduce the efficacy of therapies and increase complications. Thus, the ideal conduct should consider the classification of patients in "fit" elderly, no matter what age, suitable for more aggressive interventions, and "unifit" who should be treated with more tolerable strategies.

A major issue is the lack of specific literature about elderly BC patients. Clinical trials usually enroll young patients and, often, exclusion criteria rule out patients with comorbidities. Therefore, little is known regarding the safety and efficacy of standard treatment regimens in older patients, especially those who are aged ≥ 75 years and have other health issues [61].

A reliable decision-making tool for these patients should help to find a balance between aggressiveness of the disease, efficacy of the therapy, comorbidities and toxicities. The main problem is that medical comorbidities may increase the risk of adverse events that may decrease life expectancy rather than improve it. Comorbidities, functional impairment or mobility disability, and geriatric syndromes (including cognitive impairment) provide a reliable and accurate estimate of life expectancy as well as a comprehensive evaluation of health status [62]. However, it should be considered that the independent effect of these factors have not been well studied in older patients with BC. Nonetheless, they have been independently associated with a higher risk of surgical complications and morbidity and mortality from chemotherapy in other cancer populations [63 64].

Commonly used geriatric assessment tools could be useful. They consist in a multiparametric assessment, which includes measurement of functional, cognitive, nutritional and psychological status, comorbidities, self-assessed health status, mobility, and social circumstances [63 65]. The National Comprehensive Cancer Network Guidelines recommend that all cancer patients aged ≥ 70 years should undergo some form of geriatric assessment [66] since this can help to identify potential dangerous conditions, previously unrecognized, that can affect treatment tolerance and efficacy. Interestingly, more attention should be paid to psychological impairment (depression, in particular) that independently correlates with worse outcomes both in surgery and chemotherapy [67]. In addition, cognitive impairment must be carefully considered in decision making, because it has implications to consent to any form of treatment and increases risk from therapies such as surgery and chemotherapy [68].

In conclusion, geriatric assessment can categorize patients into three groups that correlate with life expectancy [69]. Fit patients with no significant functional impairments and/or comorbidities should receive the best evidence-based care possible. On the other end of the spectrum, older patients who are "frail" and demonstrate dependence in basic functional tasks, significantly impaired mobility, significant comorbidities, and/or at least one significant geriatric syndrome are at high risk for toxicities from cancer treatment and should be considered with extreme caution [70]. A third, more complex group, is composed of patients who are vulnerable and have concomitant mild functional or cognitive issues, well controlled and non-life threatening comorbid conditions, and/or depression. In these patients, targeted interventions can be implemented with the goal of improving outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

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