ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Seminars article

Neoadjuvant treatment for muscle-invasive bladder cancer: The past, the present, and the future

Tom J.N. Hermans, M.D.[a], Charlotte S. Voskuilen, M.D.[a], Michiel S. van der Heijden,, M.D., Ph.D.[b], Bernd J. Schmitz-Dräger, M.D., Ph.D.[c,d], Wassim Kassouf, M.D., C.M., F.R.C.S.C.[e], Roland Seiler, M.D.[f], Ashish M. Kamat, M.D., M.B.B.S., F.A.C.S.[g], Petros Grivas, M.D., Ph.D.[h], Anne E. Kiltie, M.A., D.M., D.Sc.[i], Peter C. Black, M.D., F.R.C.S.C., F.A.C.S.[j], Bas W.G. van Rhijn, M.D., Ph.D., F.E.B.U.[a,*]

[a] *Department of Surgical Oncology (Urology), Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[b] *Department of Medical Oncology, Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*
[c] *Department of Urology, Friedrich-Alexander University, Erlangen, Germany*
[d] *Department of Urology, Schön-Klinik, Nürnberg/Fürth, Germany*
[e] *Department of Surgery, Division of Urology, McGill University Health Center, Montreal, Canada*
[f] *Department of Urology, Inselspital, University of Bern, Bern, Switzerland*
[g] *Department of Urology, The University of Texas, MD Anderson Cancer Center, Houston, TX*
[h] *Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*
[i] *Department of Radiation Oncology, CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Oxford, United Kingdom*
[j] *Department of Urologic Sciences, Vancouver Prostate Centre, University of British Columbia, Vancouver, Canada*

Received 19 August 2017; received in revised form 1 October 2017; accepted 16 October 2017

Abstract

Background: Approximately half of patients who undergo radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC) will succumb to metastatic disease. We summarize the evidence for neoadjuvant radiation (NAR), chemo (NAC), and immunotherapy (checkpoint inhibition) prior to RC for MIBC.

Materials and methods: Data were obtained by a search of PubMed, ClinicalTrials.gov, and Cochrane databases for English language articles published from 1925 up to 2017.

Results: NAC usage has increased over the last decade, while NAR is rarely administered. Although NAR results in downstaging, its impact on survival is inconclusive. Based on level I evidence, cisplatin-based NAC (CB-NAC) is considered standard of care in cT2–4aN0M0 MIBC. NAC results in a 6% absolute 10-year overall survival (OS) benefit. In-depth analyses of key randomized controlled trials showed that failure to correct for uniform staging, surgical variation, and patient selection compromises the ability to identify factors predictive of response to NAC. The benefit appears to be restricted to patients downstaged to ypT1N0 or less. In these patients, 5-year OS is 80% to 90%. Regarding a number needed to treat of 17, most patients with cT2–4aN0M0 MIBC will be exposed to toxicity without benefit. Possible approaches to reduce overtreatment are suggested in this article and include patient selection, the chosen NAC regimen, and emerging molecular data to predict responsiveness to NAC. Neoadjuvant immunotherapy with checkpoint inhibitors is a promising future perspective currently under investigation.

Conclusions: Past studies on NAR show inconclusive results and NAR is rarely administered. Instead, CB-NAC is advised in eligible patients with cT2–4aN0M0 MIBC prior to RC. In the near future, predictive biomarkers will be the key to tailor the use of CB-NAC and reduce harm to nonresponders.

Keywords: Bladder cancer; Chemotherapy; Cystectomy; Immunotherapy; Neoadjuvant; Radiation

* Corresponding author. Tel.: +31 20 512 2269 / 2553; fax: +31 20 512 2459.
E-mail address: basvanrhijn@hotmail.com (B.W.G. van Rhijn).

http://dx.doi.org/10.1016/j.urolonc.2017.10.014
1078-1439/

Introduction

After radical cystectomy (RC) for muscle-invasive bladder cancer (MIBC), approximately half of patients will eventually succumb due to pre-existing metastatic disease or local recurrence [1]. In this context, many efforts have been undertaken to improve oncological outcome by adding various neoadjuvant treatment modalities to RC. Population-based data have shown that the use of neoadjuvant chemotherapy (NAC) has significantly increased over the last decade, while neoadjuvant radiotherapy (NAR) is rarely administered anymore [2,3]. Owing to inherent study limitations, the robustness of evidence for these treatment modalities can be questioned. One of the main reasons for the slow adoption of neoadjuvant treatment modalities, especially NAC, is the inability to select accurately patients who will benefit vs. those who may potentially be harmed [4]. In this review on past, present, and future neoadjuvant treatments for MIBC, we summarize the evidence and limitations of studies describing NAR (the past), NAC (the present), and immunotherapy (the future). Two timelines are presented highlighting the landmarks in bladder cancer (BC) care and those specifically for neoadjuvant treatment in MIBC (Fig. 1). We also aim to provide guidance for clinicians to further improve individualized treatment for MIBC.

The past—neoadjuvant radiation treatment

As early as 1925, Frank Kidd described the first experiences of radiation treatment (RT) for BC [5]. In 8 patients, he observed a decrease in tumor load, a relief of local symptoms or an impressive improvement in life expectancy [5]. However, many patients suffered from severe skin burns or mucosal reactions until Henri Coutard developed the principle of fractionation, the basis of current RT, in 1934 [6]. In an attempt to decrease local failure and improve survival, urologists and radiation oncologists soon began to use RT as a preoperative adjunct to RC [7].

In the 1960s–1980s, multiple efforts were made to evaluate the role of NAR plus RC in MIBC [8–10]. A meta-analysis by Huncharek et al. [11] combined the results of 751 patients from 4 RCTs assessing 5-year overall survival (OS) for NAR plus RC vs. RC alone [8,12–14]. Five-year OS favored patients who received NAR prior to RC, but this finding was not statistically significant (hazard ratio (HR): 0.71, 95% CI: 0.48–1.06) [11]. The largest RCT in this meta-analysis randomized 475 patients to NAR (45 Gy) plus RC vs. RC alone [8]. After definitive surgery, a second randomization to 5-fluorouracil or placebo was conducted. Unfortunately, only 49% of randomized patients completed the prescribed therapy and final survival analysis was conducted only in these patients. Complete pathological downstaging (pCD) to ypT0 was observed in 34% of patients undergoing NAR plus RC and 9% of those undergoing RC alone. Five-year OS in patients receiving NAR was 55% if pCD was achieved, vs. 33% for those with residual disease in the RC specimen [8]. These results are severely limited by the absence of an intention to treat analysis. Moreover, the isolated effect of NAR could not be assessed due to the use of concomitant adjuvant chemotherapy (AC). Overall, results from this trial with respect to OS were inconclusive.

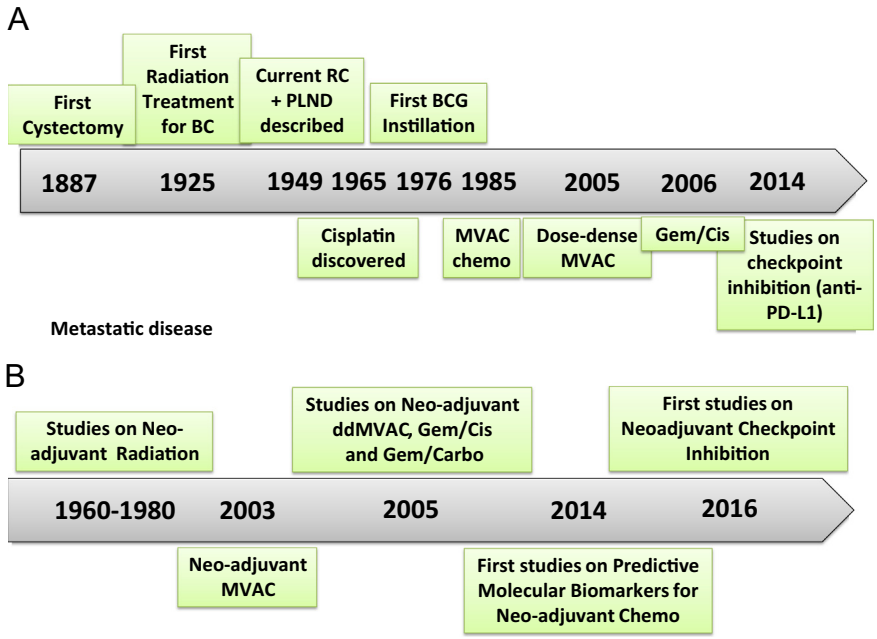

Fig. 1. (A) Landmarks in the treatment of organ-confined and metastatic bladder cancer. (B) Landmarks in the neoadjuvant treatment of muscle-invasive bladder cancer. BC, bladder cancer; BCG, Bacillus Calmette-Guérin; Gem/Cis, gemcitabine/cisplatin; MVAC, methotrexate vinblastine doxorubicin cisplatin; PLND, pelvic lymph node dissection; RC, radical cystectomy; Gem/Carbo, gemcitabine/carboplatin. (Color version of figure is available online.)