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Re: Multicenter Prospective Phase II Trial of Neoadjuvant Dose-dense Gemcitabine Plus Cisplatin in Patients with Muscle-invasive Bladder Cancer

Iyer G, Balar AV, Milowsky MI, et al

J Clin Oncol 2018;36:1949–56

Experts' summary:

This multicenter phase 2 study assessed the efficacy and tolerability of neoadjuvant dose-dense gemcitabine and cisplatin (ddGC) in 49 patients with nonmetastatic muscle-invasive bladder cancer (MIBC). Patients received six 14-d cycles of ddGC: gemcitabine 2500 mg/m² on day 1, cisplatin 35 mg/m² on days 1 and 2 (achieving a planned dose intensity of 1.875 times and 1.5 times the standard gemcitabine and cisplatin, respectively), and pegfilgrastim on day 3. Downstaging to <ypT2N0 was found in 57% of patients, but only 15% of patients had a pathologic complete response (pCR, ypT0N0). Responders (<ypT2N0) had significantly better recurrence-free survival and overall survival compared to nonresponders at median follow-up of 26 mo for surviving patients. Grade 3–4 toxicity occurred in 37% of patients, but no patient experienced toxicity-related delays to radical cystectomy (RC). The median time to RC was 6.5 wk. The authors concluded that ddGC is an active, well-tolerated neoadjuvant regimen.

Experts' comments:

Cisplatin-based neoadjuvant chemotherapy (NAC) followed by RC has become the standard of care in MIBC [1]. However, the optimal regimen in terms of both dose schedule and agents remains undefined. After the landmark SWOG-8710 trial established methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as the standard NAC regimen [2], routine clinical practice has shifted towards more modern regimens such as gemcitabine and cisplatin (GC) and dose-dense MVAC (ddMVAC) [1,3].

None of these regimens has been compared in randomised controlled trials in the neoadjuvant setting. Nevertheless, in retrospective series ddMVAC has yielded response rates similar to those after standard-dose MVAC and GC, while toxicity rates were lower [3]. Importantly, ddMVAC was associated with higher pCR and better survival rates compared to GC in a retrospective cohort of patients with locally advanced (cT3–4aN0M0) MIBC [4]. Although the superiority of ddMVAC has not been prospectively proven, these high pCR rates, higher long-term survival in the metastatic setting, and a shorter time to RC suggest that ddMVAC should be the NAC treatment of choice. Iyer and colleagues studied the efficacy of GC in a dose-dense schedule. Although limited by lack of a comparator arm, their study supports the effectiveness and tolerability of ddGC. Notably, their pCR rate was rather low (15%) even

though the majority of patients (67%) completed six cycles of NAC. Survival outcomes for patients with pCR and patients with downstaging were not reported separately, probably because of the small sample size.

Despite the lower toxicity rates for dose-dense cisplatin regimens, up to 50% of MIBC patients are considered unfit for cisplatin-based chemotherapy [1,5]. As an alternative, carboplatin-based NAC regimens have been evaluated, with response rates approaching those for cisplatin-based NAC in small retrospective series [5]. However, gemcitabine with carboplatin appeared to be inferior to cisplatin-based regimens in the metastatic setting and is therefore not recommended for NAC [1].

The application of neoadjuvant immunotherapy will probably change the established standard of care in MIBC. In the first prospective study (PURE-01) on immunotherapy in the neoadjuvant setting, 50 patients received three cycles of pembrolizumab 200 mg every 3 wk before RC [6]. pCR was achieved in 21/50 patients (42%) and downstaging to <ypT2N0 was found in 54% [6]. Although these results are promising, long-term follow-up is required to allow for assessment of survival outcomes. Several studies on different combinations of immunotherapy and combinations of immunotherapy with NAC will report findings in the next years. While we await these results, comparative studies on the efficacy of different NAC regimens and the number of cycles needed remain of major clinical importance.

Conflicts of interest: The authors have nothing to disclose.

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Re: EAU Guidelines: Prostate Cancer 2019

Mottet N, van den Bergh RCN, Briers E, et al

<https://uroweb.org/guideline/prostate-cancer/>

Experts' summary:

A long-established prerequisite for a nerve-sparing (NS) approach in radical prostatectomy is a low risk of extracapsular extension (ECE) of prostate cancer [1]. Traditionally, ECE risk has been assessed preoperatively on the basis of clinical and pathological variables for prostate biopsy. In the 2017 European Association of Urology (EAU) guidelines, Partin tables are recommended for deciding on NS; however, these provide a probabilistic ECE risk estimation without information on laterality or acting as decision rules, and thus are inconclusive for guidance on surgical dissection.

The EAU guidelines changed their recommendation in the 2018 version, suggesting referral to side-specific and externally validated nomograms. This recommendation is retained in the updated 2019 version, and includes cT stage, International Society for Urological Pathology grade, nomograms, and multiparametric magnetic resonance imaging (mpMRI) to guide an NS approach.

Experts' comments:

How can we definitively predict ECE risk and avoid positive surgical margins? According to a systematic review [2], only four nomograms have been developed for side-specific prediction. External validation (EV), even if recommended, cannot guarantee the generalizability of a model [2]. This is the case for Partin 1997, the most popular nomogram used to date, with a total of 2092 PubMed citations [2]. Despite the abundance of EVs, Partin tables perform poorly when translated to a European setting, and are thus of limited value for distant and different data sets [2]. Indeed, it is recognized that EV outcomes are often ambiguous as they are affected by temporal, geographic, and domain limitations [2].

Moving toward 2019, it would be anachronistic not to consider how urological practice has changed in view of mpMRI. Nevertheless, mpMRI sensitivity for predicting ECE is still only at 0.57, so even if it is attractive, the role of mpMRI added to existing models or included in novel nomograms is still controversial [3].

Keeping in mind how the NS recommendation has evolved over time, what should we expect in the future? The 2019 guidelines are beginning to suggest post hoc analysis or preoperative mpMRI to guide these decisions [1,4]. Given the limits of mpMRI, intraoperative frozen sections may represent a more reliable source of information to develop

such guidance [1]. A NeuroSAFE (neurovascular structure-adjacent frozen-section examination) approach has been advocated, but its widespread use is limited by costs and the need for a fully equipped laboratory. The recent advent of ex vivo confocal microscopy seems an opportunity to provide a NeuroSAFE-like approach, with a lower organizational burden and real-time diagnosis of freshly excised tissue, that could be suitable for surgical requirements [5].

In view of the novel decade, a combined approach involving surgical preplanning and intraoperative microscopy-based tailoring could be a further cornerstone for extending the implementation of safe NS approaches in radical prostatectomy.

Conflicts of interest: The authors have nothing to disclose.

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