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Words of Wisdom

Re: Immediate Versus Deferred Chemotherapy After Radical Cystectomy in Patients with pT3-pT4 or N+ M0 Urothelial Carcinoma of the Bladder (EORTC 30994): An Intergroup, Open-label, Randomised Phase 3 Trial
Sternberg CN, Skoneczna I, Kerst JM, et al

Lancet Oncol 2015;16:76–86

Experts' summary:
This phase 3 trial conducted by the European Organization for Research and Treatment of Cancer compared adjuvant versus deferred cisplatin-based combination chemotherapy after radical cystectomy (RC) in patients with extravesical (pT3–pT4) or node-positive urothelial carcinoma of the bladder (UCB). A total of 284 patients were randomized at a 1:1 ratio. Adjuvant chemotherapy (AC) did not significantly extend overall survival (OS; hazard ratio [HR]: 0.78; 95% confidence interval [CI], 0.56–1.08; $p = 0.13$), although progression-free survival was longer (HR: 0.54; 95% CI, 0.4–0.73; $p < 0.0001$).

Experts' comments:
Unfortunately, the trial did not complete the final accrual target of 660 patients and thus joins a long list of incomplete or underpowered randomized trials evaluating the value of AC for muscle-invasive but resectable UCB. The investigators also reported an updated trial-level meta-analysis ($n = 949$) that demonstrated an OS benefit for AC (HR: 0.77; 95% CI, 0.65–0.91; $p = 0.002$). Large retrospective studies, most notably a recent large analysis of 5653 patients, have demonstrated that AC extends OS in those with extravesical and/or node-positive disease [1]. However, retrospective studies are inherently confounded by patient selection biases that cannot be accounted for.

In contrast, definitive evidence exists to support neoadjuvant cisplatin-based combination chemotherapy for resectable (cT2–T4aN0M0) UCB [2]. The SWOG trial, which may be considered the single most relevant trial because it administered conventional methotrexate, vinblastine, doxorubicin, cisplatin chemotherapy preceding RC, demonstrated an extension of OS (HR: 0.67; two-sided $p = 0.06$) regardless of baseline clinical stage (cT2N0 vs T3–4N0).

Although definitive phase 3 data supporting AC are lacking, these data in aggregate suggest that AC may be an acceptable alternative to neoadjuvant chemotherapy (NC). Despite a trend for increasing use of NC, AC and NC are still used in similar numbers of patients [3]. Proponents of AC argue that initial RC and pathologic staging affords optimal prognostic stratification, and opponents argue that roughly 30% of patients may not qualify for AC owing to poor recovery from postoperative complications within 90 d [4]. However, the possibility that NC may provide superior OS compared with AC has not been considered, which is biologically possible because NC delivers systemic chemotherapy 3–4 mo earlier than the AC approach to those with lethal distant micrometastases. Consequently, NC should remain the preferred strategy at this time. Perhaps it is time for a randomized trial comparing NC and AC.

Conflicts of interest: Guru Sonpavde's institution receives research support from Bayer, Boehringer-Ingelheim, and Onyx; he is a consultant for Merck, Bayer, Sanofi, Genentech, Pfizer, Argos, and Novartis. Sumanta Pal is a consultant for Pfizer, Novartis, Genentech, Aveo, Glaxo-Smith-Kline, Eisai, and Cerulean and has received honoraria from Genentech.

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http://dx.doi.org/10.1016/j.eururo.2016.03.057

Re: Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

Galsky MD, Stensland KD, Moshier E, et al

J Clin Oncol 2016;34:825–32

Expert's summary:

Galsky et al used the National Cancer Data Base to assess the benefit associated with adjuvant chemotherapy for bladder cancer following radical cystectomy. They identified 5653 patients diagnosed with pT3–4 or node-positive disease at radical cystectomy who had not been exposed to neoadjuvant chemotherapy, representing approximately 70% of all newly diagnosed bladder cancer cases in the United States from 2003 to 2006. Of the patients, 1293 (23%) had received adjuvant chemotherapy. By applying propensity scores and sensitivity analyses, the authors were able to account for a variety of baseline characteristics that could affect treatment allocation between the groups. Their findings reflected a significant overall survival advantage favoring adjuvant chemotherapy (hazard ratios ranging between 0.61 to 0.72, depending on the model applied).

Expert's comments:

Several undisputable facts guide our clinical approach to muscle-invasive bladder cancer (MIBC). First, it often manifests as systemic disease at presentation (despite the absence of overt clinical and/or radiographic metastasis), thus ideal management should combine both local and systemic therapies. Second, the most effective local therapy is bladder removal and extended pelvic lymph node dissection. The optimal systemic regimen should include platinum-based chemotherapy in eligible patients. Third, based on two large prospective randomized trials [1,2] bolstered by a well-executed meta-analysis [3], the administration of chemotherapy in a neoadjuvant setting should be considered the standard of care, conferring a 5–10% overall survival advantage.

With this in mind, it remains perplexing how, as of 2010, only 40% of patients with MIBC had been exposed to perioperative chemotherapy, only half of which was administered in a neoadjuvant form [4]. Possible explanations for underutilization of neoadjuvant chemotherapy might include fear of overtreating seemingly localized cancer, thereby exposing those who might have been cured by surgery alone to unwarranted toxicity, and the lack of definitive evidence to support treatment in an adjuvant setting [5]. The latter is accentuated in light of three clinical trials that addressed this question terminating prematurely because of poor accrual. Regardless of cause, the lack of adequate therapy targeting the systemic component of the disease for those in need will likely result in suboptimal cure rates. By using a national (rather than institutional) database and applying sophisticated statistical methodology to overcome some of the selection biases inherent in retrospective analyses, Galsky and colleagues provided strong, compelling evidence demonstrating a clear survival advantage with immediate postoperative chemotherapy in patients with pT3–4/N1 bladder cancer.

Taken together, perioperative chemotherapy should be sought in most, if not all, patients with MIBC. In the absence of comparative data, platinum-based neoadjuvant therapy remains the practice of choice, whereas for those preferring a risk-adapted approach, the use of adjuvant chemotherapy should be strongly encouraged in the setting of adverse pathologic features. The results of a phase 3 adjuvant trial assessing the role of the programmed death ligand 1 inhibitor atezolizumab in advanced bladder cancer are awaited eagerly.

Conflicts of interest: The author has nothing to disclose.

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http://dx.doi.org/10.1016/j.eururo.2016.03.058

Re: DNA-repair Defects and Olaparib in Metastatic Prostate Cancer

Mateo J, Carreira S, Sandhu S, et al

N Engl J Med 2015;373:1697–708

Expert's summary:

Mateo et al [1] report the results of a phase 2 trial in which 50 patients with metastatic castration-resistant prostate cancer (CRPC) were treated with olaparib tablets. All patients were treated with chemotherapy and 49 patients received either enzalutamide or abiraterone. Sixteen of 49 evaluable patients had a response which was defined as an objective response according to Response Assessment in Solid Tumors 1.1 or a reduction of $>$ 50% in prostate-specific antigen or a reduction in circulating tumor-cell count from $>$ 5 to $<$ 5 cells per 7.5 ml of blood. Twelve of 16 patients received