Published Ahead of Print on November 10, 2014 as 10.1200/JCO.2014.58.0498
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.58.0498

Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Neoadjuvant Chemotherapy in Bladder Cancer: Ready for Prime Time?

TO THE EDITOR: Choueiri et al[1] and Plimack et al[2] recently reported results from two phase II trials using dose-dense (or accelerated) methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) as neoadjuvant chemotherapy (NAC) in muscle-invasive urothelial cancer. Evidence of the benefit of NAC on disease-free and overall survival of patients as compared with cystectomy alone were obtained with regimens that are currently no longer used, such as standard MVAC (sMVAC) or methotrexate, vinblastine, and cisplatin. Thus refining the optimal cytotoxic combination is an important need for daily practice since no phase III study has been conducted so far with the most currently used combinations, such as ddMVAC or gemcitabine and cisplatin (GC).

The two prospective studies published in *Journal of Clinical Oncology* provide rather reassuring results.[1,2] After three to four cycles of ddMVAC, the pathologic downstaging ($\leq$ pT1N0M0) was quite similar (49% and 53%), including pathologic complete response rates (pT0) ranging from 26% to 38%, respectively. Concomitantly, a large majority of patients achieved the planned number of cycles without any life-threatening toxicity. Unfortunately, biomarker studies (ERCC1, telomere length, and p53 mutation) did not demonstrate any correlation with response, toxicity, or survival. Although these results, along with other (retrospective)[3] experiences, point in the right direction to consider ddMVAC as an interesting option for NAC, several issues remain to be solved.

Patient Selection

NAC was typically validated in patients with cT2-cT4 N0 disease and a normal renal function, allowing the use of standard doses of cisplatin. Patients with N1 (i.e. locally advanced) disease do require upfront chemotherapy rather than NAC. In patients with impaired renal function, NAC has not been validated and is therefore not indicated in daily practice. Forty-three percent of patients in the study by Choueiri et al[1] had N1 disease, and 30% of patients had a calculated creatinine clearance less than 60 mL per minute in the study by Plimack et al.[2] Such heterogeneity may affect the significance of the results.

Optimal Schedule of Chemotherapy

The appropriate cisplatin dose intensity required for optimal efficacy is unknown. Switching from sMVAC to ddMVAC has resulted in the doubling of the dose intensity from 17.5 to 35 mg/m^2/wk without a clear increase in the pathologic downstaging. Similarly, in a French retrospective study studying the outcome of patients treated with sMVAC (median, three cycles) or ddMVAC (median, four cycles) in 16 centers from 2004 to 2012, the pathologic downstaging turned out to be roughly equivalent (60% and 53% among 45 and 166 patients, respectively).[4] In the same way, the optimal cumulative dose of cisplatin, that is, the total number of cycles of NAC, remains to be determined. Limiting the number of cycles to three (210 mg/m^2) might be enough considering the results reported by Plimack et al.

Relationship Between Pathologic Downstaging and Survival

The pathologic downstaging is used as a surrogate end point. Although the pT0 status at cystectomy has been reported to confer a clear survival benefit,[4-6] not all patients can be considered cured. The primary objective of NAC is to increase overall survival. In comparison with experience in other primary tumors, three cycles could be in this way insufficient to obtain a survival benefit. A randomized phase II study investigating NAC using ddMVAC or GC is planned through Southwest Oncology Group. However it will not help further define the optimal regimen in terms of survival benefit. A multicenter, phase III study is ongoing in France in patients with cT2-cT4 N0 disease and normal renal function, comparing six cycles of ddMVAC and four cycles of GC (i.e., 3 months of NAC in each arm) with progression-free survival as primary end point.

Molecular Correlates of Response

Finally, and perhaps most importantly, it is often stated that identification of biomarkers predictive of response would help select the patients most likely to benefit from NAC. Until now, most studies have concentrated on the assessment of one genetic marker, and none of them has allowed the validation of a reliable marker for daily practice.[1,2,7] Currently, the most relevant approach seems to lie in the identification of molecular subtypes using whole-genome gene expression profiling.[8]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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DOI: 10.1200/JCO.2014.58.0498; published online ahead of print at www.jco.org on November 10, 2014

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Consulting or Advisory Role: Roche, Sanofi, Astellas, Lilly, Pfizer
Research Funding: Roche (Inst), Amgen (Inst), Lilly (Inst), Oncogenex (Inst), Sanofi (Inst)
Travel, Accommodations, Expenses: Sanofi, Novartis

Hélène Gauthier
No relationship to disclose

Camille Serrate
No relationship to disclose

Christian Pfister
No relationship to disclose

Stephane Culine
No relationship to disclose