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Paper Alert

Optimal Perioperative Chemotherapy for Muscle Invasive Bladder Cancer

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Since the landmark publication by Grossman et al. [1] neoadjuvant chemotherapy (NAC) with a combination of Methotrexate, Vinblastine, Adriamycin (doxorubicin) and cisplatin (MVAC) demonstrated a 5% advantage in overall survival (OS) compared with radical cystectomy (RC) alone, NAC followed by RC has become standard of care for managing muscle invasive bladder urothelial cancer (MIBC) in patients "able" and willing to undergo RC and cisplatin containing NAC [2]. Even prior to the publication of Grossman, et al's article in 2003, the toxicity of MVAC for advanced or metastatic disease had led to a search for less toxic regimens and Gemcitabine-Cisplatin (G-C) appeared to have similar efficacy but lower toxicity than MVAC for more advanced disease [3]. Other modifications of each regimen to lower toxicity (for both NAC and advanced disease) led to regimens such as "accelerated" MVAC [4] and "dose dense" MVAC (dd MVAC) [5] and "dose dense" G-C [6]. Moreover, NAC, while standard of care, given its modest benefit and real toxicity, has often not been utilized even in eligible patients, and adjuvant chemotherapy for extravesical disease after RC (stages pT3, T4 or Tany N1-2) without prior NAC has also become popular [7].

With these issues in mind, a recently reported prospective randomized trial of ddMVAC vs G-C in peri-operative treatment of MIBC (cT2-T4, NO for NAC, and pT3, T4 and/or N1,2 for adjuvant therapy) is of interest [8]. Patients received 6 two-week cycles of ddMVAC vs 4 three-week cycles of G-C, in part to equalize the durations of treatment. The primary endpoint was progression free survival (PFS) (given that the vast majority of participants were disease-free after cystectomy, this would be similar to disease free survival) or death from any cause within 3 years. 493 patients with similar demographics and a median age of 63 years (patients older than age 70 were not included) were randomized and over 80% in each group were male. Almost 90% in each group chose NAC (rather than adjuvant therapy) with over 90% in each group receiving NAC having cT2 NO disease. Cystectomy was not performed in a little less than 10% in each arm. However, the primary end point, PFS at 3 years, while favoring ddMVAC (64% vs 56%) was not significantly in favor (HR = 0.77 (95% CI 0.57 to 1.02; $p = 0.066$). If one looked only at the 88% who received NAC, ddMVAC (66% vs 56% for PFS) was now significantly superior (HR 0.70 (95% CI 0.51 to 0.96; $p = 0.025$). Similarly, in both NAC and adjuvant groups, time to progression was significantly delayed in those receiving ddMVAC (HR = 0.68, 95% CI 0.5 to 0.93, $p = 0.017$), particularly for those receiving NAC (HR = 0.62, 95% CI 0.44 to 0.87, $p = 0.005$). Medium OS had not been reached at 40-month follow-up but again favored ddMVAC. Surgical complications were similar in both arms of those receiving NAC, and pathologic endpoints after NAC were similar for pTO and surgical margin rates.

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However, more than twice as many ddMVAC patients did not complete their full course of NAC chemotherapy (41.4% ddMVAC vs 16.2% for G-C). This was a toxic regimen. In standard practice 4 cycles of ddMVAC is given [4, 5], not 6 cycles as in this study.

So, what have we learned from the VESPER trial? While perioperative ddMVAC did not meet the primary endpoint in both groups of patients, it did in the NAC cohort which comprised nearly 90% of participants. However, the regimen of ddMVAC used in this study is not standard, delivering two extra cycles and 50% more cisplatin than the G-C group (or patients getting standard ddMVAC NAC) received. Whether this is extrapolatable to bladder cancer care in the United States (or elsewhere) both in terms of toxicity or efficacy is unclear. Moreover, with additional systemic agents now being effective for advanced bladder cancer, including immunotherapies, antibody-drug conjugates and targeted therapies, it is no surprise that studies combining these agents with chemotherapy are already underway [9].

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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