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Re: Comparison of Population-based Observational Studies with Randomized Trials in Oncology

Soni PD, Hartman HE, Dess RT, et al

J Clin Oncol 2019;37:1209–16

Experts' summary:
In a recent issue of the *Journal of Clinical Oncology*, Soni and colleagues [1] published an interesting analysis comparing the results of population-based observational studies and randomized trials in oncology. The authors identified 350 observational cancer treatment comparisons and matched these to 121 corresponding randomized trials. They found that while 62% of the hazard ratios derived in observational studies fell within the 95% confidence interval of the corresponding randomized trial, there was no significant correlation between the hazard ratio estimates of observational studies and randomized trials.

Experts' comments:
The results of this analysis differ from most previous attempts to examine differences in outcomes between observational studies and randomized trials. Summarizing previous analyses on this methodologic topic, a recent Cochrane review concluded "there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions" [2].

We must therefore ask what differs between this analysis and previous ones. Have more recent observational studies in oncology become less rigorous than observational studies in other fields from decades past? While possible, it seems less likely that this analysis simply demonstrates the well-recognized efficacy-effectiveness gap [3]. Many authors, including the senior author of the paper by Soni et al [4], recognize that there are massive disparities in randomized trials in oncology. This means that patients eligible for the trial significantly differ from the population of patients that they are purported to represent on the basis of age, race, socioeconomic status, and comorbidity. One of the most relevant in oncology trials may be the exclusion of patients with any prior malignancy; according to data from the US National Cancer Institute, approximately one in six patients diagnosed with cancer each year have previously been diagnosed with a different cancer. In the context of non–small-cell lung cancer, Al-Baimani et al [5] demonstrated that 78% of patients treated at their center would be deemed ineligible for a trial. However, 46% of these patients received such systemic therapy. As a result, even when assessing the same question, the population included in observational studies and randomized trials in oncology probably differ. Among 283 randomized trials, the vast majority (83%) had at least one poorly justified exclusion criterion and 37% of all exclusion criteria were poorly justified [6]. These exclusions are even more common in industry-sponsored trials.

Thus, while randomized controlled trials have the greatest internal validity of any study design, their lack of external validity may explain differences between conclusions from observational studies and randomized studies in oncology. To allow for more informative extrapolation of trial results to patients treated in everyday urology and oncology practice, clinical trialists should limit exclusion criteria such that the trial population reflects the general population of patients with the disease.

Conflicts of interest: The authors have nothing to disclose.

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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/m^2 on day 1, cisplatin 35 mg/m^2 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, doxorubicine, 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 pembroluzimab 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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