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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring New and Emerging Treatments in Muscle Invasive Bladder Cancer

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Plimack:
Hi, I'm Dr. Elizabeth Plimack here at Fox Chase Cancer Center where I'm the Deputy Director and a GU Medical Oncologist. And this is CME on ReachMD. Today, I'll be discussing new and emerging therapies in muscle invasive bladder cancer.

So, muscle invasive bladder cancer is localized and curable, but based on the biopsy, we can see that the tumor is invading into the muscle wall of the bladder. This is a sign that the tumor is prone to metastases and therefore, the standard of care for this stage of disease is neoadjuvant therapy, followed by surgical resection for cure.

In terms of neoadjuvant regimens, dose-dense MVAC is the preferred regimen and gem/cis is an alternative regimen. Gem/carbo is not used. However, this standard is set to change with the advent of newer effective therapies now being tested in this space.

Here's a slide summarizing some of the current perioperative trials. They all have a few things in common. All enrolled patients with MIBC, they are randomized 1 to 1 or 1 to 3, depending on how many arms, to either a novel combination or a chemotherapy alone, or in some cases, no neoadjuvant chemotherapy. Then, everyone gets a cystectomy and in the novel arms, in the experimental arms, everyone gets the same therapy again postoperative as a sandwich approach. So, we call these sandwich approaches that are being tested.

You can see the studies, here, are testing pembrolizumab and enfortumab/vedotin, which is a novel combination of an ADC with an immunotherapy. And then, two of them test gemcitabine and cisplatin with checkpoint inhibitors, pembrolizumab in one study, durvalumab in another. I'll be focusing on the NIAGARA study, because that's the only one that has reported results so far. And these were reported at ESMO.

I will just comment that one of the controversies about the sandwich trial design is that adjuvant therapy is given to everyone regardless of pathology and cystectomy. That means we are probably overtreating the pathologic complete response patients who would not normally qualify for adjuvant as part of a study. And we may be incorrectly treating patients with futile therapy if their tumor has already shown progression through that therapy in the neoadjuvant space. And this has come up a number of times, but this is how the studies were done, and we will interpret the data with that in mind.

So, moving on to the NIAGARA results, you can see by these Kaplan Meier curves that the combination of durvalumab plus gem/cis followed by durvalumab after cystectomy versus gem/cis alone, neoadjuvant only, with either observation or adjuvant or standard of care subsequent, did show a benefit. So, at 24 months we see, in terms of event-free survival, 73.5 percent of patients were event-free compared to 67.9% on the chemo-only arm. This is significant with a hazard ratio of 0.69.

What this tells us is that if gem/cis is being considered, it should be used in the NIAGRA sort of design where you add durva to the

gem/cis neoadjuvant and then be sure to follow-up adjuvant for everyone with the 8 cycles of durvalumab afterwards. I would not extrapolate this study to say you can just add durva to the neoadjuvant and skip the adjuvant. You really should do the full approach because that's what the data are based on, the sandwich approach.

Another really encouraging result from NIAGARA is– the pathologic complete response rate at surgery. So, again, this is the percent of patients who had no tumor in their bladder at resection. I'll focus on the right-hand panel, the reanalysis, which I think is the more robust analysis. And this shows a pathologic complete response of 37.3% in the durvalumab combination arm, and 27.5% in the comparator arm. A clear benefit, although I think many of us were hoping to see something a little bit better, as I'll show you in the next slide, a pathologic complete response of 37.3%, while better than gem/cis in this study, is really on par with how neoadjuvant chemotherapy alone without immunotherapy and without necessarily an adjuvant component has performed.

So the top-line results for the durva pre-post plus gem/cis sandwich approach. That's again, the experimental arm in NIAGARA. And if you look, you can see that the results we see in terms of pathologic complete response rate, 1-year metastasis-free survival, 2-year metastasis-free survival, and 2-year overall survival almost exactly match those that were achieved with dose-dense MVAC as neoadjuvant only, with no adjuvant component specified and no immunotherapy in the VESPER study.

So, taking this new NIAGARA data into consideration, my recommendation is that if you plan to use gem/cis, you should add durva to it week 3 and add on 8 cycles post-cystectomy. But if MVAC is something that you typically use, you can achieve the exact same results using dose-dense MVAC neoadjuvant only. You're done sooner, you save immunotherapy for later if needed, either in the adjuvant space or in the metastatic setting.

That's all the time we have for now. This is Elizabeth Plimack. Thanks for joining me on CME on ReachMD.

Announcer:
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