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How Do ADCs Improve Patient Outcomes in Patients With Urothelial Cancer?

Announcer:
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Dr. Koshkin:
Hello everybody, my name is Vadim Koshkin. I'm a genitourinary medical oncologist and assistant professor at the University of California San Francisco. This is episode two, how to antibody-drug conjugates improve patient outcomes in patients with urothelial cancer. This episode in particular focuses on the antibody-drug conjugate or ADC mechanism of action. Here are the relevant components of an antibody-drug conjugate. There is of course the antibody which attaches to a specific target present on the cancer cell. There is the linker that then links this antibody to the payload, which is the usually the cytotoxic chemotherapy drug, which is in the end what destroys the cancer cell and leads to its death.

A good target of an antibody-drug conjugate has to be highly expressed on the surface of cancer cells, while having lower or preferably a lack of expression on normal tissues. Nectin-4 is an example of a good target. This is the target of enfortumab vedotin, which is preferentially expressed on the surface of urothelial cancer cells and not expressed in most other tissues. This slide in particular demonstrates the expression of Nectin-4 in tumors of patients in EV-201 one of the clinical trials of enfortumab vedotin. On the x-axis, we have the each bar represents an individual patient. On the y-axis is the H-score of Nectin-4 expression at baseline. H-score is a way of measuring expression of a particular protein. In this case, the highest score possible is 300. As you can see on the slide, most patients with advanced urothelial cancer have pretty high expression, and the majority, or actually essentially all the patients have at least some expression, which again is what makes this a good target.

But to be an effective antibody-drug conjugate this drug has to do more than just effectively attach to the target. Once it attaches to the target, and effective antibody-drug conjugate is internalized into the cancer cell where the drug is actually broken up the cleavable linker connecting the antibody to the payload chemotherapy is severed or removed. And the chemotherapy is released to then lead to cancer cell death through usually, well, in this case, cell cycle arrest and tumor cell apoptosis. The release of the payload chemotherapy here is critical because the chemotherapy can then diffuse across cell membranes into surrounding cancer cells as well and lead to their death. Those particular cells may actually have lower or non-existent expression to a particular target. Yet, this allows for still the targeted delivery of this particular drug through the tumor microenvironment while limiting its delivery to other tissues. And again, this is something that's known as the bystander effect.

The payload is also critical. This is of course the chemotherapy drug portion of the antibody-drug conjugate. It is responsible for cancer cell killing after this targeted delivery. And of course, this mechanism of action can vary as they do with chemotherapy drugs in general. These payload agents can be microtubule disrupting agents as is the case with enfortumab vedotin for instance, or topoisomerase inhibitor as is the case with sacituzumab. And of course, other mechanism of action can also be possible. All payloads are not created equal. They have different mechanisms of action, therefore different potential mechanisms of resistance. They also have accounts for different toxicities, and that becomes important in considering which patients to treat with a particular antibody-drug conjugate. Finally,

some may be more immunogenic than others. And that is something we address in the next slide.

Here's some of the data that's discussed by Dr. Galsky at ASCO. Looking at the differences in outcomes, and specifically response rates of the different combinations of antibody-drug conjugates with immunotherapy drugs. And the pattern that comes across here is when combining an antibody-drug conjugate with an MMAE payload, this taxing payload with an immune checkpoint inhibitor. The response rates are quite robust and significantly higher than the response rate with the antibody-drug conjugates alone. On the other hand, in combining checkpoint inhibitors with antibody-drug conjugates with different payload, the topoisomerase payload. You don't see as higher response rate and in fact the response rates seeing for instance, combining nivolumab with trastuzumab deruxtecan or pembrolizumab with sacitizumab govitecan are only slightly higher than the response rates you see with the drug alone, with the antibody-drug conjugate alone, I should say. All this suggests that there may be something about the particular payload drug that accounts for potentially superior activity when combined with an immune checkpoint inhibitor. Suggesting potentially that there is some immunogenicity associated with this payload drug. And that is of course, something that should be looked into further.

In summary, antibody-drug conjugates allow for targeted delivery of cytotoxic drugs to cancer cells. This is their advantage over conventional cytotoxic chemotherapy. Consequently, they potentially mitigate treatment-related toxicities by limiting some of these off-target effects, which we generally do see with cytotoxic chemotherapy. These drugs are consequently potentially better tolerated but are still very effective and they're still cytotoxic options. I consider this as a targeted chemotherapy rather than a non-chemotherapy option. The targets and payloads, it should be pointed out vary significantly among the different antibody-drug conjugates. This accounts for their different efficacy and also toxicity profiles. It is important to consider that the bystander effect can lead to differential toxicities and also can affect combination strategies with other drugs like immunotherapy agents. Thank you for your attention. This concludes the current episode.

Announcer:
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