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What Is the Therapeutic Rationale for ADCs in Cancer?

Announcer:
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Dr. Hurvitz:
Hello, my name is Sara Hurvitz. I'm from UCLA and today I'm talking about what is the therapeutic rationale for antibody-drug conjugates in cancer. While chemotherapy has been shown to be effective and it's been used for more than 70 years for cancers of all types, it is limited by toxicity to normal non-cancer cells due to the non-selective nature of chemotherapy. Therefore, scientists sought ways to selectively deliver chemotherapy to cancer cells using a protein antigen that is uniquely expressed or over-expressed on cancer cells compared to normal cells. One way to selectively target a tumor antigen is to develop an antibody that perfectly matches the antigen or is able to bind to that antigen like a lock and key.

The antibody can then be loaded with chemotherapy, so that the chemotherapy is delivered to the tumor cell only when the antibody is bound to the tumor antigen. This is the idea behind antibody-drug conjugates or ADCs. Some people use the analogy of a Trojan horse or a smart bomb as a description of how ADCs work. ADCs are comprised of the antibody shown in this picture as the blue structure, where the Fab portion binds to the tumor antigen and the Fc portion sticks out. There is then a cytotoxic payload that is connected to the antibody shown in the orange on this graphic. And then there is a linker that connects the antibody to the payload. Now each of these three components is required in an ADC, but they can all differ in different ADCs in this class of agents. Some antibodies will bind to HER2 or TROP-2, for example. So the antigen that the antibody binds to can differ from ADC to ADC. The payload itself, the chemotherapy that is tagged on can differ and even the linker can be different.

Some are cleavable linkers, some are non-cleavable linkers. And so each of these components can change the effects or the activity or the toxicity of a given ADC. In fact, in some payloads are membrane permeable and are able to leave the cancer cell and kill nearby tumor cells if they are membrane permeable and this is called a bystander effect. In addition, the number of cytotoxic payloads attached to each antibody, is known as the drug antibody ratio or DAR and that can differ from ADC to ADC.

So here's a picture showing how ADCs work. In step 1, the antibody that is carrying the chemotherapy, is bound to the antigen that is expressed uniquely on tumor cells. In step 2, the ADC connected to the antigen is internalized to the early endosome. In step 3, this becomes a full lysosome where the linker is cleaved and the cytotoxic payload is released and is able in step 4 and 5, to do its work and kill the cancer cell.

The first example of an ADC that was successfully developed and FDA-approved for breast cancer, was trastuzumab emtansine or T-DM1. This is a picture showing how this works. T-DM1 is a HER2 targeted antibody that is linked to a maytansinoid chemotherapy. The chemotherapy is not released in the bloodstream limiting the toxicity. When the T-DM1 ADC is linked onto HER2, the entire complex is internalized and once within the lysosome, the linker is cleaved and the maytansinoid is able to do its work as a microtubule poison.

This drug was FDA-approved in 2013 based on the results of EMILIA, which showed that T-DM1 was more effective than standard

chemo given with Lapatinib, a HER2 targeted tyrosine kinase inhibitor. This approval made T-DM1 the standard second-line treatment for HER2 positive metastatic disease.

The KATHERINE study also demonstrated benefits with T-DM1, but for early stage breast cancer, when used in patients who had residual disease after standard chemotherapy and trastuzumab in the neoadjuvant setting. As you can see, T-DM1 was better than standard trastuzumab when given in the adjuvant setting for these high-risk patients with a significant improvement in invasive disease free survival. One feature of T-DM1, is that it really requires a high expression level of HER2 to be active because it doesn't have any bystander effect. The chemotherapy stays and works on HER2 positive cancer cells.

In contrast, some ADCs are developed that have a bystander effect whereby the cytotoxic payload is able to escape the tumor cell that has that antigen expressed and kill nearby cells that may have lower expression of that tumor antigen. One example of that is Trastuzumab Deruxtecan or TDXT. This is an ADC comprised of a HER2 targeted antibody linked to a topoisomerase 1 inhibitor or chemotherapy, which is an exatecan derivative. This ADC has a drug antibody ratio of 7:8, which is higher than with T-DM1, and the payload can leave the cancer cell and kill nearby cancer cells, which is what's called a bystander effect. The bystander effect can also cause more toxicity, given the fact it is a less selective ADC.

This drug was shown in the DESTINY-Breast-O4 to be significantly better than T-DM1 for HER2 positive metastatic breast cancer, making this drug the new standard of care in the second-line setting and beyond.

On the next slide, you see another ADC that targets an antigen called TROP-2. This is Sacituzumab Govitecan and this drug similar to Trastuzumab Deruxtecan, has a topoisomerase 1 inhibitor payload, but the antibody itself is targeting an antigen called TROP-2.

The ASCENT study indicated that this drug was better than standard chemotherapy for patients with metastatic triple-negative breast cancer, leading to its FDA approval.

So in summary, the field of antibody drug conjugates has significantly altered the treatment landscape for those who are diagnosed with cancer. This class of medications is allowing patients to be treated with high doses of very potent chemotherapies with greater efficacy and without the same level of toxicity as would be seen if the chemotherapy was given naked or alone. It's a very exciting time given the number of ADCs now available to patients with even more promising agents to come. Thank you so much for your attention.

Announcer:
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