ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Breast Cancer in Focus

Immunoconjugates in the Treatment of Breast Cancer

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H&O What immunoconjugates are available?

DT In 2011, the US Food and Drug Administration (FDA) approved brentuximab vedotin (Adcetris, Seattle Genetics) for use in patients with Hodgkin lymphoma who are not candidates for autologous stem cell transplant, and for patients with anaplastic large cell lymphoma that has failed to respond to at least 1 multiagent chemotherapy regimen. Brentuximab vedotin is an anti–CD30-targeting drug that is bound to a receptor that is expressed on lymphoid cells.

In 2013, the FDA approved trastuzumab emtansine (TDM-1; Kadcyla, Genentech), an immunoconjugate that binds the human epidermal growth factor receptor 2 (HER2), for use in patients with HER2-positive metastatic breast cancer who previously received trastuzumab or a taxane. Trastuzumab emtansine contains the same antibody that is in trastuzumab (Herceptin, Genentech), linked to the highly potent antimicrotubule agent emtansine. Trastuzumab emtansine has been shown to be effective in patients who have progressed on the standard therapies for HER2-positive breast cancer, which include trastuzumab plus chemotherapy and the tyrosine kinase inhibitor lapatinib (Tykerb, GlaxoSmithKline).

I would estimate that 10 or 15 immunoconjugates are in active clinical trials, and of course more are being developed in the laboratory.

H&O What are some of the most important studies of trastuzumab emtansine?

DT The approval of trastuzumab emtansine was based on the results of EMILIA (An Open-Label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer). This study found that trastuzumab emtansine was effective in patients who had progressed on trastuzumab plus chemotherapy. Although the agent was not curative, it prolonged survival and time to progression compared with a standard second-line regimen of the HER1/HER2 tyrosine kinase inhibitor lapatinib plus capecitabine.

Another important study, with Dr Sara Hurvitz as the first author, looked at trastuzumab emtansine in the first-line setting. Although the agent is not approved for this indication, this phase 2 study showed that it may perform slightly better than chemotherapy plus trastuzumab in terms of time to progression, and with fewer side effects.

An important phase 3 trial called TH3RESA was recently published in the *Lancet Oncology*. In TH3RESA, trastuzumab emtansine significantly increased the length of time before the disease worsened compared with treatment of physician's choice in women with advanced HER2-positive breast cancer whose cancer had recurred or progressed despite previous treatments. Some of the women in the study had been through 3, 4, or 5 different treatments, including trastuzumab and lapatinib, and the study showed that even these patients responded to trastuzumab emtansine better than to trastuzumab combined with several different chemotherapy agents. The results of TH3RESA tell us that we can use trastuzumab emtansine even in patients who have had multiple prior therapies.

H&O How do immunoconjugates work?

DT Immunoconjugates deliver highly toxic drugs selectively to cancer cells (see the figure). Each immunoconjugate has 3 basic components. The first component

is an antibody or a peptide; the 2 agents that have been approved so far contain an antibody that recognizes an antigen on the surface of a cell. The second part of the drug is the linker; this is a small chain of molecules that links the antibody or peptide to the drug and releases the toxin upon internalization to the tumor cell. The third component is the toxin absorbed by the cell, which causes cell death with just a few molecules.

A major advantage of these agents is that they do not rely on blocking a specific biological pathway in order to work; they contain potent chemotherapy agents that will kill any cell with only a few molecules. Most of the drugs that are used with immunoconjugates target the microtubule, which serves the important function of pulling the chromosomes apart during mitosis, the second phase of cell division. When mitosis is disabled, the cell stops growing and has no option but to die.

Similar to the immunoconjugates are the radioimmunoconjugates, in which highly radioactive particles—either yttrium-90 or iodine-131—are attached to antibodies. The antibodies allow high doses of radiation to be delivered directly to cancerous cells. So far, 2 of these have been FDA-approved for use in lymphoma: ibritumomab tiuxetan (Zevalin, Spectrum) and iodine I-131 tositumomab, which is no longer available.

H&O How long have immunoconjugates been in development?

DT The first immunoconjugates were created approximately 30 years ago. The development of these agents was slowed at first by the high rate of side effects. Many of these side effects were caused by failure of the linker; the drug was coming unhooked from the antibody and circulating freely. This was causing a lot of toxicities, especially liver toxicity; the liver would take up the drug because it has receptors that bind antibodies. Another problem was that the antibodies that were initially used in the 1980s and 1990s were of mouse origin. In some people, the immune system would view the antibodies as foreign proteins and would mount an immune response against them. Not only have we progressed from using mouse antibodies to human antibodies over the past 5 or 6 years, we also have much better linker chemistry.

H&O What other advances have occurred?

DT When a receptor is bound by an antibody or a peptide, it becomes internalized—the membrane invaginates and brings into the cell the moiety that is attached to the receptor. The little pocket that forms is called the lysosome. Lysosomes have a microenvironment, including the pH, that is different from that of the rest of the cell. Many of these immunoconjugates are designed to release the toxin when the pH drops, but earlier generation immunoconjugates were releasing the toxin too soon. The currently used linkers are more stable to reflect the actual physiology of the lysosome and release the toxin at the right time so that it enters the cell and does not leak out. As a result, the immunoconjugates have much less toxicity.

Each immunoconjugate is different; the efficacy depends to a large degree on what antibody-antigen pair is used and how tumor-specific and abundant the antigen is. Some are more successful than others; I think that as more antibodies are developed we will see a combination of winners and losers. Trastuzumab emtansine is one of the agents that is effective and has a very good safety profile.

H&O What makes trastuzumab emtansine different from other types of treatment for metastatic breast cancer?

DT Trastuzumab emtansine does not have the side effects of chemotherapy; patients typically do not experience hair loss, nausea, vomiting, or fatigue. At the same time, it has the effectiveness of a chemotherapy drug—it has more activity than any drug we know of in patients who are refractory to multiple HER2-targeting drugs.

H&O What are the limitations of immunoconjugates?

DT The first limitation is that sometimes some of the normal cells are targeted because the antigen to which these drugs are directed is not 100% tumor specific. The second limitation is that sometimes the antigen is not expressed at high enough levels in the cancer cell or not enough of the drug binds to the target, which can reduce the effectiveness of the drug. The third limitation is that the toxin may inadvertently be released in normal cells, causing side effects to occur.

For example, trastuzumab emtansine causes neuropathy in rare cases, because a small amount of the trastuzumab may get out into the blood and cause injury to normal tissues. A small amount of the drug is also taken up by megakaryocytes, which can interfere with the production of platelets and lead to thrombocytopenia.

H&O I imagine that cost would be another potential issue with these agents?

DT Yes, cost is an issue. Trastuzumab emtansine can cost nearly $10,000 a month, which is extremely high. Most insurance companies cover trastuzumab emtansine as long as it is used according to the FDA indication, but even then the copays can be too high for some patients.

The National Institute for Health and Care Excellence, which advises the National Health Service in the United

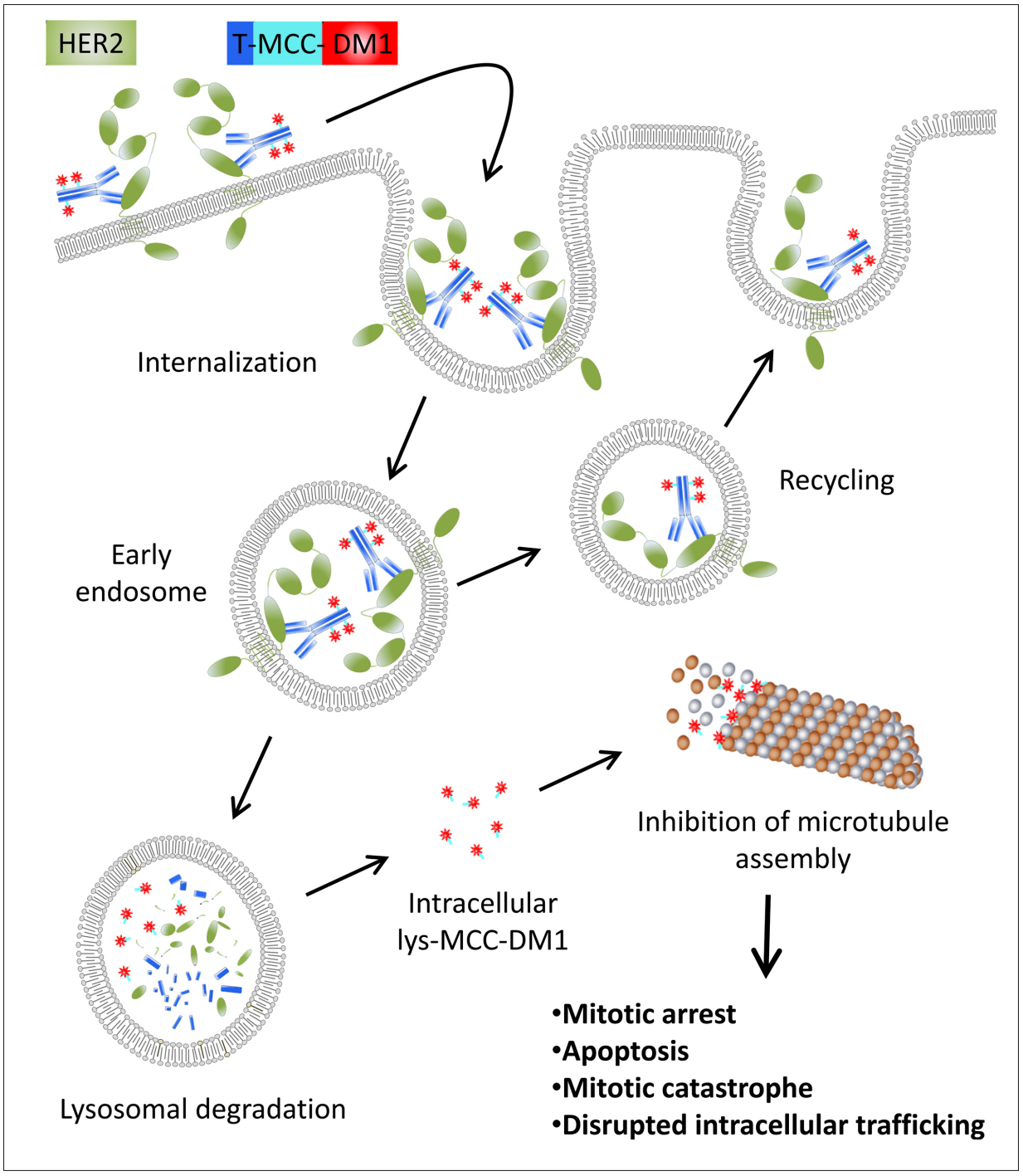

Figure. Intracellular trafficking of trastuzumab emtansine (T-DM1). Binding of trastuzumab emtansine onto human epidermal growth factor receptor 2 (HER2) on the plasma membrane is followed by entry of the HER2-T-DM1 complex into the cell via receptor-mediated endocytosis. Internalized endocytic vesicles form early endosomes. The load of early endosomes can be recycled back to the cell membrane or the early endosome can mature to a lysosome. Release of DM1 occurs as a result of proteolytic degradation of the antibody part of T-DM1 in the lysosomes. Intracellular lysine (lys)-MCC-DM1 inhibits microtubule assembly, causing mitotic arrest, apoptosis, mitotic catastrophe, and disrupted intracellular trafficking.

MCC, the linker (N-maleimidomethyl)cyclohexane-1-carboxylate.

Kingdom, recommended against covering trastuzumab emtansine because it did not meet their criteria for approval. Their criteria are that the quality-adjusted number of life-years saved does not cost more than £50,000 per year. The group uses a fairly complicated formula to calculate quality of life along with quantity.

H&O What are some of the challenges in manufacturing these agents?

DT One challenge is manufacturing the antibodies, which is not easy to do and requires a special reactor. Another challenge is finding the right linker; several effective linkers are available but further improvements should be made over time. As far as the toxic agent is concerned, monomethyl auristatin E is used in brentuximab vedotin and has been used in several of the other immunoconjugates.

Other challenges come with testing these agents; it can be difficult to conduct large, randomized trials, especially for diseases or mutations that are uncommon. Finding the right dose and schedule also can be a challenge. We have to fine-tune our use of these agents, and develop rules for people who have side effects.

H&O What should be the focus of future development efforts?

DT Certain aspects of immunoconjugates need to be improved. The way to develop the best immunoconjugate is to find an antigen that is specific to the cancer. There are a handful of tumor antigens out there, but very few of them are fully tumor-specific. Even HER2 is expressed in normal cells, so it is not fully tumor-specific.

Amgen is developing a drug called AMG 595 that targets a variant protein called EGFRvIII. This protein is seen only on cancerous cells, primarily in glioblastomas and other brain tumors. AMG 595 is composed of an EGFRvIII-specific antibody bound to DM1, and is being tested in glioblastomas and select other cancers. I think we will see a new generation of immunoconjugates that are designed to attack cancer-specific proteins. We still have to learn why some of these agents work while others do not.

Suggested Readings

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