EDITORIALS

The Promise of Antibody–Drug Conjugates

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The promise of antibody–drug conjugates (ADCs) is the specific targeting of highly potent cytotoxic agents to malignant disease without adversely affecting normal tissues. We may be on the verge of fulfilling that promise. This moment has been more than 25 years in the making and has required technology development in every facet of the conception and execution of ADCs. In this issue of the *Journal*, Verma et al.[1] describe the positive results of their phase 3 trial comparing the ADC trastuzumab emtansine to the combination of lapatinib and capecitabine in women with advanced breast cancers that are strongly positive for human epidermal growth factor receptor 2 (HER2). The demonstration of significant clinical benefit (in terms of progression-free survival [3.2 months] and overall survival [5.8 months]) in favor of the ADC for patients whose breast cancers progressed after therapy with treatment regimens containing trastuzumab is noteworthy from both clinical and pharmacologic perspectives. From a patient's viewpoint, substantially enhanced drug effectiveness (as compared with the standard of care) was achieved despite a relatively modest profile of serious adverse events that avoids many typical side effects of cytotoxic regimens, except for a higher frequency of thrombocytopenia, which resolved in most patients with dose modification.

The first ADCs targeted antigens with insufficient tumor-cell selectivity, used mouse antibodies that were immunogenic, and carried drugs that lacked potency. Early anticancer drug conjugates also used linkers that were unstable and bound variable numbers of drug molecules to the antibody protein, resulting in heterogeneous mixtures being administered to patients.[2] The approval by the Food and Drug Administration (FDA) of brentuximab vedotin (Seattle Genetics) for the treatment of refractory Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma[3] and the positive outcome of the EMILIA trial[1] may be the initial output from a pipeline of ADCs that are about to reach clinical practice.

The pharmacologic properties of trastuzumab emtansine that appear to have been confirmed by this trial are impressive. Objective evidence of tumor shrinkage indicates, as previously reported in animal models, that HER2 receptor number and function remain intact in most patients in whom clinical resistance to trastuzumab has developed, allowing specific binding of the trastuzumab emtansine conjugate (T-DM1).[4] The remarkable rate of breast-cancer regressions observed at sites of visceral metastases suggests, as originally hypothesized, that the cytotoxic maytansinoid portion of the conjugate is delivered intracellularly at sufficient concentrations to produce cell death (and consequent tumor shrinkage) consistent with mitotic catastrophe, rather than inducing the cytostasis commonly associated with single-agent trastuzumab. The beauty of T-DM1 is that conjugate formation does not preclude the antibody-dependent cellular cytotoxicity or HER2-neutralizing activity of the antibody; thus, T-DM1 retains the functions of trastuzumab and adds the effects of a potent cytotoxic drug.[5]

There are approximately 25 ADCs in oncology clinical trials and more in preclinical development.[2,6] The best ADC protein targets have abundant expression on cancer cells and very limited expression on other cells; patients whose tumors express high target levels are most likely to benefit from ADC treatment. ADCs require

that the antibody–target protein complex internalize in the target cells where the drug molecules are released. ADCs are among the most tumor-selective anticancer therapeutics but are not the most efficient for drug delivery; thus, potent drugs are required. The maytansinoids (such as T-DM1)[5] and dolastatin analogues (such as brentuximab vedotin)[2] target tubulin and suppress microtubule dynamics. These molecules have in common extreme potency with growth-inhibitory properties reached in the picomolar concentration range; thus, ADCs are "targeted" to deliver potent cytotoxic agents.[7]

Trastuzumab emtansine is currently under review by the FDA for women with advanced breast cancer that has progressed after treatment with trastuzumab. In view of the efficacy and excellent safety profile of this agent, the ongoing randomized trial evaluating use in the first-line setting (ClinicalTrials.gov number, NCT01120184), and the many other studies examining trastuzumab emtansine across a broad range of disease contexts, it seems likely that a major shift in our basic approach to the treatment of HER2-positive cancers is imminent. This new approach will almost certainly incorporate trastuzumab emtansine, as well as a more general appreciation and acceptance of the use of ADCs in the routine care of patients with solid-tumor cancers. The development of preclinical and clinical data on ADCs will provide guidance for the next generation of these agents, with better targeting and improved linkers that may carry many more drug molecules. The largest remaining challenge may be in identifying the most specific and appropriate tumor-cell surface proteins to target. With the understanding that ADCs are chemotherapeutics that will be used in combination treatment regimens, the time may have arrived for this technology to become a major contributor to improved cancer therapy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1211736

Statins and Cancer-Related Mortality — Let's Work Together

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In this issue of the *Journal*, Nielsen et al.[1] provide data suggesting that statin use in Denmark has caused a substantial decline in all-cause and cancer-related mortality. Collectively, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most commonly prescribed class of drugs worldwide, and after two and a half decades of use, this therapy has been credited with declines in cardiovascular events[2] at the cost of some common side effects (myalgia and diabetes) and some that are rare (elevated liver enzyme levels and rhabdomyolysis).[3] Previous studies focusing on statins and the incidence of cancer have provided only weak or no evidence of a modest reduction in rates of selected cancers.[4]

The enviable network of national databases in Denmark, which track and link deaths, cancer diagnoses, and medications, was used to generate data on statin use by individual patients in the entire Danish population, including 295,925 patients who received a diagnosis of cancer between 1995 and 2007. The study design provides substantial power to evaluate mortality from even less common cancer types, with limited selection bias and guaranteed generalizability, at least to Denmark, since virtually the whole population is represented in the databases.