Antibody-drug conjugates (ADCs) are composed of three primary components: the antibody, the linker, and the cytotoxic drug (Fig. 1A). In this issue of *Clinical Cancer Research*, Ikeda and colleagues (1) report on the generation and testing of ADCs directed against CD138, which is expressed on multiple myeloma (MM). The authors use maytansinoids, which bind to microtubules in a manner similar to the Vinca alkaloids, as the cytotoxic component of their ADC constructs and show that anti-CD138-maytansinoid ADCs can be effective in xenograft models of MM.

In theory, ADCs provide a means to increase the effectiveness of chemotherapy by targeting the drug to neoplastic cells while reducing side effects (2, 3). Several maytansinoid conjugates are now in the clinic. The most advanced compound is trastuzumab-MCC-DM1 (T-DM1), which uses the antibody component of Herceptin (Genentech Inc., South San Francisco, CA) (trastuzumab, anti-Her2) and a thioether linker (4). Based on favorable phase II data, this ADC is now in phase III clinical testing for women whose breast cancers have progressed after Herceptin-based therapies.

In this issue of *Clinical Cancer Research*, Ikeda and colleagues (1) show that anti-CD138-maytansinoid conjugates are potent against MM models. The authors describe their studies with three different linkers, two cleavable by disulfide reduction (SPP and SPDB) and another nonreducible thioether linker that is used in T-DM1 (MCC also referred to as SMCC), and conclude that anti-CD138(nBT062)-SPDB-DM4 is the most promising clinical candidate. This work nicely shows the underlying principle of how ADCs can increase the therapeutic potential of chemotherapy. *In vivo*, the anti-CD138 ADCs are efficacious whereas neither the anti-CD138 antibody or the maytansinoid alone have any effect on the tumor at equivalent amounts of drug and antibody. This effect is specific to the targeting of the antibody, because a control ADC that does not bind the cells is not efficacious. The authors further show that the anti-CD138 ADCs can overcome the protective effects of cytokines and bone marrow stromal cells, both in vitro, and in a model in which MM containing bone fragments are engrafted into SCID mice. Although other ADCs directed against other MM targets using these linker-drugs have proven efficacious in xenograft models (5), these data with CD138 are encouraging because not all targets are equal. The quality of any particular ADC target is usually dictated by an assessment of the target’s differential expression on tumor versus normal tissue. An exception to this is when the target is expressed on a dispensable tissue or the target is only expressed on tissues that are insensitive to the conjugated drug. In addition, how the target-ADC complex is trafficked inside the cell can make a large difference both to the efficacy of the ADC and what linkers will be effective (6); some ADCs are not effective or require the use of reducible linkers owing to low expression or inappropriate trafficking of their targets (7). CD138 seems favorable in this regard in that anti-CD138(nBT062)-SMCC-DM1 was effective, albeit at higher doses than the reducible linker ADCs SPP-DM1 and SPDB-DM4. CD138 has the additional virtue of being expressed, although not highly over expressed, on the surface of almost all MM cells regardless of whether the patients are previously treated for MM (5, 8). Thus, anti-CD138 ADCs could be of use in the vast majority of MM patients.

One aspect of critical importance in assessing the potential of an ADC in the clinic is its safety and tolerability. In other words, does the ADC have the necessary therapeutic index so that it can be safe and effective? There are several mechanisms by which ADCs can induce toxicity (Fig. 1B, see ref. 3): (1) release of free drug or other toxic metabolites into circulation through intrinsic instability of the linker or release of free drug or toxic metabolites from targeted cells; (2) nonspecific uptake by cells that do not express the antigen; and (3) the targeting of the ADC to normal tissue expressing the relevant antigen.

From our current understanding, the target-independent related toxicities for anti-CD138(nBT062)-SPDB-DM4 might be expected to be manageable because SPDB-DM4 ADCs are presently in the clinic. The most relevant data were obtained with anti-CanAg-SPDB-DM4 (IMGN242, huC242-DM4) showing this ADC can safely be dosed up to 3.4 mg (of ADC)/kg.
Chemotherapies, a linker that is stable in circulation that may be cleaved once near or inside the cancer cell, and an antibody specific to a target on the tumor cell surface. B. Mechanisms of tumor killing and effects on normal cells. ADCs can kill tumor cells in several ways: one is by the targeting of the tumor and releasing the drug or other toxic metabolites, another is the release of free drug or metabolites from the targeted cells thus killing other nearby tumor cells (bystander effect). There also may be some efficacy from the nonspecific release of free drug and toxic metabolites into circulation. These free cytotoxic compounds can also impact susceptible normal tissue. In addition, normal tissue can be affected by specific targeting owing to expression of the target or nonspecific uptake of the ADC.

A limitation of our understanding of anti-CD138(nBT062)-SPDB-DM4 is the lack of data assessing its target-dependent safety. CD138 has a relatively broad expression pattern including the basolateral surface of epithelial cells, vascular smooth muscle cells, and the endothelium (see ref. 9 and references therein). Expression patterns for CD138 were confirmed using the parent antibody of nBT062 B-4 in an immunohistochemistry screen (10). Of particular concern is skin and gut epithelial expression of CD138 because serious skin toxicity was observed with anti-CD44v6 bivatuzumab mertansine probably owing to CD44v6 expression in this tissue (11). Unfortunately, this risk will be challenging to evaluate preclinically because anti-CD138(nBT062) does not bind cynomolgus monkey CD138, the closest species (to human) commonly used in preclinical safety studies (10). Perhaps using a surrogate SPDB-DM4 ADC that is capable of binding nonhuman primate CD138 should be considered to allay this concern.

The past decade has seen significant improvements in the treatment of MM. However we have yet to achieve cures as a clinical outcome for this devastating disease (12), and an effective chemotherapy would comprise a therapeutic strategy that may bring that goal within reach. Anti-CD138(nBT062)-SPDB-DM4 or other ADCs may have the potential to be an effective therapy for MM.

**References**


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