regulatory T cells, also are plausible but require further investigation.

Few modifiable risk factors for HL have been identified, and the scientific evidence is insufficient to conclude that either UVR or vitamin D is related to HL risk. However, the results of this pooled study should catalyze further research into UVR and HL. In addition to molecular studies, further epidemiologic research that can address key methodologic issues such as consideration of HL subtypes, recall bias, and integration of personal behaviors, occupational exposures, and ambient UVR has the greatest potential for shedding light on the etiology of HL.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES


LYMPHOID NEOPLASIA

Comment on Deckert et al, page 3500

In the spotlight: a novel CD37 antibody-drug conjugate

M. Lia Palomba1 and Anas Younes1

MEMORIAL SLOAN-KETTERING CANCER CENTER

In this issue of Blood, Deckert et al make a strong argument in favor of IMGN529, a novel anti-CD37 maytansinoid antibody-drug conjugate (ADC), elegantly showing its activity against B-cell lymphoma in vitro and in vivo preclinical studies.1

CD37 is a member of the transmembrane 4 superfamily of tetraspan proteins, which consist of 4 potential membrane-spanning regions, 2 extracellular loops and 2 short intracytoplasmic tails.2 Although most tetraspanins are ubiquitous proteins, CD37 expression is nearly exclusively limited to mature B cells and B-cell-derived lymphoid malignancies. B-cell early progenitors, T cells, natural killer cells, and myeloid cells exhibit only minimal amounts of membrane-associated CD37. This relative lineage restriction makes CD37 a suitable target for immunotherapy.

In the late 1980s, a 131I-labeled anti-CD37 monoclonal antibody was developed for human use, resulting in significant responses in patients with B-cell non-Hodgkin lymphoma (NHL).3 Further developments were hampered by the success of rituximab and other anti-CD20–directed therapies, and CD37 was put on the back burner for several years. However, one of the most remarkable innovations in targeting the CD37 antigen emerged a few years ago with the development of a CD37-specific small modular immunopharmaceutical,4 an engineered protein that includes anti-CD37 variable regions linked to an immunoglobulin-constant domain. The CD37–specific small modular immunopharmaceutical demonstrated robust antitumor activity against lymphoid malignancies in preclinical studies, including in human lymphoma xenograft models. Its humanized counterpart, TRU-016 (otlertuzumab), has similar activity in preclinical models, was shown to have synergistic activity in combination with other agents, and is currently being evaluated in a randomized study in combination with bendamustine compared with bendamustine alone in patients with chronic lymphocytic leukemia (CLL) experiencing relapse. An Fc-engineered anti-CD37 monoclonal antibody, in which the Fc portion of the antibody is altered to enhance affinity for FcγRIIIα, is also in early development.5 Finally, another CD37-directed therapeutic currently under investigation in humans is betalutin, a 122I-labeled anti-CD37 antibody.6 Ultimately, the superiority of one of these compounds over the others will strictly depend on its ability to exert potent antitumor activity by engaging multiple pathways of cytotoxicity.

ADCs are complex engineered molecules composed of an antibody linked via a stable linker to a potent cytotoxic drug or payload, which preferentially kill tumor cells while sparing toxic effects on healthy tissues. Once the ADC binds to its cell surface target, it is internalized, releasing the toxic payload inside the cell. In general, the payload of ADCs is either a DNA binder (calicheamicin) or a tubulin binder. There are 2 major classes of tubulin binders: maytensins and auristatins. Within the maytensins, DM1 and DM4 are currently being used, with different potency and toxicity profiles. The brentuximab vedotin payload is an aurostatin derivative, whereas the trastuzumab emtansine payload is a DM1 maytensin.8 Other conjugates are also being explored, including chemotherapy agents (see table).

The strong efficacy of the poster children of ADCs, brentuximab vedotin and trastuzumab emtansine, resulted in their being approved by the US Food and Drug Administration (FDA) for relapsed Hodgkin lymphoma and anaplastic large-cell lymphoma, and for metastatic breast cancer, respectively. Other ADCs currently being

From www.bloodjournal.org by guest on August 15, 2017. For personal use only.
evaluated for the treatment of hematologic malignancies are listed in the table.

The ADC used in this study by Deckert et al comprises a humanized anti-CD37 antibody, K7133A, linked via a SMCC [N-succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate] linker to the maytansinoid DM1 payload. DM1 exerts its antitumor effect by depolymerizing microtubules and arresting the cells in prometaphase/metaphase. The authors go on to dissect in detail the antitumor mechanism of the DM1-conjugated antibody (IMGN529), demonstrating that the conjugated compound retains the same strong immune effector activities as the unconjugated K7133A. When the naked K7133A and IMGN529 were compared in cytotoxicity assays, the cytotoxic potency induced by IGMM529 was far superior compared with the naked antibody, with induction of cell death in a dose-dependent manner in the picomolar range. Mice inoculated with a human B-cell lymphoma cell line receiving single doses of IMGN529 had a better tumor-free survival time than mice treated with the unconjugated antibody or with rituximab, confirming the additive effect of DM1 delivery. B-cell depletion was observed in the treated animal, and it was more profound than that induced by rituximab treatment.

Given these results, IMGN529 seems to be a promising drug, and certainly the planned first-in-man clinical trial is warranted. Overall, the success of trastuzumab-emtansine, as well as that of brentuximab vedotin, suggests that ADCs might take a spotlight in the current landscape of antitumor drugs.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

**REFERENCES**


© 2013 by The American Society of Hematology
In the spotlight: a novel CD37 antibody-drug conjugate

M. Lia Palomba and Anas Younes

Updated information and services can be found at:
http://www.bloodjournal.org/content/122/20/3397.full.html

Articles on similar topics can be found in the following Blood collections
  Free Research Articles (4644 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml