Multidrug Resistance in Acute Myeloid Leukemia: Potential New Therapeutics

In acute myeloid leukemias (AMLs), multidrug resistance (MDR) is frequently, but not always, caused by the MDR1 gene product, a 170- to 180-kDa glycoprotein known as P-glycoprotein (Pgp) or human MDR1 protein (1). It is characterized by broad resistance to several structurally, chemically, and pharmacologically distinct chemotherapeutic compounds. Many theories explain how Pgp affects MDR, including the “drug pump” model, in which Pgp hydrolyzes adenosine triphosphate to actively pump drugs out of the cell (2,3). As many MDR cells have been found to have increased intracellular pH and decreased plasma membrane potentials, another explanation of the MDR mechanism of Pgp is the altered-partition model. This model takes into account how the alterations in intracellular pH and membrane potential that accompany the overexpression of Pgp indirectly affect the partitioning of the drugs, but Pgp does not directly pump the drugs out of the cell (4–6). Other drug-resistance proteins, which are associated with hematologic cancers that use similar mechanisms, include the MDR-associated protein, the lung resistance protein, and the breast cancer resistance protein (7).

Many investigators working to improve cancer therapy have tried to use various immunologic approaches to killing cancer cells because such approaches might circumvent chemotherapeutic drug resistance. One of the assumptions of an immunologic approach is that cells that are resistant to chemotherapeutics should not be cross-resistant to immunotherapy because the mechanisms of action are so widely different. Unfortunately, several groups have shown that MDR cells seem to be resistant to several forms of immunologic therapies, including complement-mediated cytotoxicity (5,6), immunotoxin, gelonin attached to monoclonal antibodies (mAbs) (8), interleukin 2 (9), and drug immunoconjugates (10–12).

Another immunologic treatment is the use of mAbs to deliver radioisotopes directly to the tumor cells. At the present time, the use of radiolabeled antibodies in the treatment of AML, with Pgp expression has not been well studied, if at all. In this issue of The Journal of Nuclear Medicine, Kersemans et al. (13) use a strategy to overcome MDR using mAbs that have been labeled with $^{111}$In modified with a nuclear localizing sequence (NLS). They showed that the addition of the peptide sequence CGYPKKKRKVGG, which contains the NLS PKKKRKV of SV-40 large T-antigens, allowed the antibody to be internalized and to translocate to the nucleus. Once in the nucleus, Auger electrons from the $^{111}$In were cytotoxic to the parental HL60 cell line and drug-resistant (mitoxantrone-insensitive) HL60-MX-1 cell line and to the primary AML specimens that were expressing a diversity of MDR phenotypes. These results suggest that $^{111}$In-anti-CD33 mAbs that are modified with an NLS may be a new treatment for patients who have drug-resistant myeloid leukemias.

Although there have been significant advances in the treatment of AML, only 20%–30% of these patients reach long-term disease-free survival (14). The addition of Pgp expression predicts an even poorer prognosis in the elderly, those patients who have relapsed, and patients with secondary AML (11,15).

When considering radioimmunotherapy for the treatment of any type of cancer, one must keep in mind three important factors: the target tumor, isotope, and antibody (16). Because leukemias are easily accessible and have well-defined differentiation antigens, they are ideal for the use of radiolabeled antibodies (17). AML is characterized by the expression of CD13, CD15, CD33, and CD117 (18). CD33 is a 67-kDa cell-surface glycoprotein found on myeloid leukemia cells and on committed myelomonocytic and erythroid progenitor cells. It is not found on lymphoid, nonhematopoietic, or mature myeloid cells, making CD33 a prime target for antibody binding (19,20).

Different isotopes have been attached to antibodies based on their half-life and the type of particle they emit. For single-cell kill, with the least cytotoxicity to normal cells, the ideal isotope emission should have a path length that is the same as that of the target cells (21). $^{90}$Y and $^{131}$I emit $\beta$-particles, which have a relatively long range and a low linear-energy transfer. Unfortunately, these properties make $\beta$-particles an excellent choice for solid tumors but not for hematologic cancers, in which antibodies cannot bind to all the tumors cells at sufficient levels (21). This long particle range results in the irradiation of target tumor cells as well as surrounding cells, causing normal cells to be killed. Alpha-particles, on the other hand, have a shorter range...
have levels of antigen that are comparable to those expressed in the cell lines. Kersemans et al. (13) reported that the HL-60 and HL-60-MX-1 cells contained $3.4 \times 10^4$ CD33 per cell. With this number of sites per cell, they determined that at a specific activity of 8 MBq/µg, 10% of the radioactivity is localized to the cell surface, 70% is in the cytoplasm, and 20% is in the nucleus. It has been previously reported that myeloid and monocytic leukemias contain only $1 \times 10^4$ CD33 per cell (27). A possible drawback with CD33 as the target is that these levels can be decreased among different cell lines and in patient samples, preventing enough Auger electrons from entering the nucleus to kill the cell. To overcome these lower CD33 levels of different targets, a higher specific activity may be needed to increase the percentage inside the nucleus. However, this could reduce immunoreactivity. Another aspect to consider is the pharmacokinetics of the antibody with the attached polypeptide chain; are they different from those of the antibody alone? Pharmacokinetics must be determined for these novel constructs.

The attachment of the NLS to the antibody may invigorate interest in radioimmunotherapy and seems to have many applications. The use of γ-emitters on NLS-tagged antibodies is noteworthy. The NLS-tagged antibody could bring the isotope directly to the nucleus to ensure a “direct hit.” Possible problems associated with α-particle emitters such as $^{212}$Bi and $^{213}$Bi are the short half-lives, making it difficult for an antibody to reach the tumor cells in time to have an effect, and the longer path lengths, affecting some normal bystander cells (21). The issue of short half-life could be solved by using $^{225}$Ac, which has a half-life of 10.5 d (28). To reduce the killing of normal cells, the NLS on the antibody would bring the α-particle directly to the nucleus of the cancerous target, and less antibody would be required.

The addition of the NLS to a radio-labeled antibody, allowing it to enter the nucleus and increase the killing of multidrug-resistant cells, is promising. The results demonstrated in the article by Kersemans et al. (13) show that there may be a treatment to overcome MDR in AML and perhaps other types of hematologic cancers.

Jeffrey H. Weisburg
Yeshiva University
New York, New York

REFERENCES


**Erratum**

In the article “SPECT/CT,” by Buck et al. (*J Nucl Med.* 2008;49:1305–1319), the legends of Figures 1, 5, and 6 contain errors. In the legend of Figure 1, “99mTc-iodobenzamide” should be “123I-ioflupane (DaTSCAN [GE Healthcare]).” In the legend of Figure 5, panel B is described as a 99mTc-MIBI scan but is in fact a 99mTc-pertechnetate scan. In the legend of Figure 6, “99mTc-MIBG” should be “123I-MIBG.” The authors regret the errors.
Multidrug Resistance in Acute Myeloid Leukemia: Potential New Therapeutics

Jeffrey H. Weisburg

Published online: August 14, 2008.
Doi: 10.2967/jnumed.107.050153

This article and updated information are available at:
http://jnm.snmjournals.org/content/49/9/1405

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml