

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma and Myeloma

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## Drug Resistance in Hematologic Malignancies

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**H&O** Does drug resistance happen more frequently in certain hematologic malignancies?

**WD** Drug resistance is a greater problem in those hematologic malignancies that are not curable. Patients with incurable hematologic malignancies, such as myeloma or a low-grade lymphoma, will eventually develop drug resistance, at which time their disease progresses.

**H&O** Could you describe the mechanism by which drug resistance develops in hematologic malignancies?

**WD** The mechanisms of drug resistance are determined by the disease and the drug, as well as by whether it is acquired or de novo resistance. Acquired resistance occurs over time following multiple therapies, while de novo resistance occurs before the disease is ever exposed to chemotherapy.

The focus in this column is on de novo drug resistance, which can develop through an intrinsic mechanism associated with the disease itself, usually a mutation, that would confer a survival advantage in a certain population of cells. In such cases a patient will be initially treated with an agent and respond, sometimes even experiencing a complete response; then the disease will relapse. After the relapse, the disease is now drug-resistant. A mutation in a particular protein could have created a survival advantage for some malignant cells and allowed them to survive the initial therapy, but there is a new and exciting alternative mechanism that we are exploring related to the microenvironment. In the case of hematologic malignancies, we are specifically interested in the bone marrow

microenvironment, which could act as a sanctuary for the malignant cells during initial exposure. The idea that the microenvironment can influence drug response is a new and exciting area, because understanding mechanisms by which the environment protects malignant cells provides new targets for therapy.

**H&O** Is this work on drug resistance new?

**WD** Research on drug resistance began 20 years ago with P-glycoprotein. It was suspected that this single protein could confer multi-drug resistance in different tumor types, and because many hematologic malignancies express the P-glycoprotein gene, it was believed that the hematologic malignancies could be prototypes for drug resistance. The P-glycoprotein gene is responsible for transporting a number of chemotherapy drugs out of the cell, which prevents the agents from killing the cell. It was theorized that simply turning off that gene would prevent drug resistance.

Although P-glycoprotein is important, we subsequently learned that eliminating that mechanism of resistance only leads to other mechanisms. Furthermore, because of the complexity we have found with acquired drug resistance, we now understand that it will be more effective to prevent resistance instead of treating it. This understanding has led to a focus on de novo resistance that we didn't appreciate 20 years ago. We can now have a much more profound impact on drug resistance upfront.

**H&O** What are some drug-specific resistances?

**WD** One of the more notable examples of drug-specific resistance is that which arises with imatinib mesylate (Gleevec, Novartis) as a result of a mutation in BCR/ABL, which is the agent's target.

**H&O** What can be done for a patient whose hematologic malignancy has acquired drug resistance?

**WD** When a patient's disease becomes drug resistant, therapies that act in a unique, target-specific way are needed. However, the cell can still adapt to acquire resistance to that new targeted therapy, and if enough cells are not killed on initial therapy, then drug resistance clones

will emerge and the disease will eventually progress. For this reason, the challenge is to gain the greatest amount of efficacy on initial therapy.

We described this phenomenon in myeloma in 2003, in a study in which we performed phenotypic and genotypic analysis of acquired versus de novo resistance to melphalan (Alkeran, GlaxoSmithKline). We found that the de novo resistance was far less complex, both genotypically and phenotypically. So to increase the efficacy of treatment, we need to address de novo mechanisms of resistance and, we hope, even prevent the more complex acquired resistance phenotype.

**H&O** So the goal of research on drug resistance is to gain the greatest amount of efficacy on initial therapy?

**WD** The ultimate goal is to prevent drug resistance from occurring. Greater understanding of de novo drug resistance will lead to more efficacious initial therapies, which will reduce the likelihood of developing acquired drug resistance in the first place.

**H&O** Are drug resistant models used in the identification of drug targets?

**WD** The classic way to identify drug targets in hematologic malignancies is to use developed cell lines from patients. Using in vitro techniques with these cell lines, we try to discern what mechanisms of resistance may occur, then we move to animal models both to examine the mechanisms of resistance and to develop means of overcoming or preventing such resistance. Animal models can be very helpful for examining the role of the microenvironment, providing invaluable insight into what to study in patients.

### Suggested Reading

Hazlehurst LA, Enkemann SA, Beam CA, et al. Genotypic and phenotypic comparisons of de novo and acquired melphalan resistance in an isogenic multiple myeloma cell line model. *Cancer Res.* 2003;63(22):7900-7906.

Dalton WS. The tumor microenvironment: focus on myeloma. *Cancer Treat Rev.* 2003;29(suppl 1):11-19.

Matsunaga T, Takemoto N, Sato T, et al. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. *Nat Med.* 2003;9(9):1158-1165.

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