Clinical Trials

Dismounting the MDR horse

Edward Libby and Robert Hromas

P-gp (also termed MDR1, or multidrug resistance-1) is a member of the membrane ATP cassette family that mediates efflux of several drugs commonly used to treat AML. Its expression has been correlated with an adverse outcome, which was thought to occur because it mediates resistance to chemotherapy. However, recent studies have suggested that inhibiting P-gp might improve outcome in AML. This is based on the idea that P-gp inhibition could specifically enhance remission rates and subsequent survival in elderly patients (> 65 years) who have increased P-gp levels on their leukemia cells compared with younger patients. A well-designed trial showed that zosuquidar because it targeted the wrong efflux proteins, or with the intensity of staining for these efflux proteins. This addresses the possibility that there was no benefit from zosuquidar because it targeted the wrong efflux protein. These data imply that the increased expression of P-gp in poor-prognosis AML is probably not the cause of the poor prognosis, but the result.

This carefully performed study lays to rest the concept that inhibition of ATP cassette drug efflux can improve outcome in AML. Thus, further efforts in this area should be rapidly redirected to other potential treatment options. It is discouraging that zosuquidar did not have any benefit, as elderly AML is indeed an area that dearly needs better therapy. Nonetheless, the value of this study is that it will allow resources to be directed elsewhere. Thus, although this is a negative study, it is still important, in that it has been done carefully, and therefore should settle this hotly debated question of whether drug efflux inhibitors can improve outcome in AML.

Resources for clinical trials are finite, and closing the door on controversial questions may be as important as positive results. Investigators all too often ask the same question in slightly different ways. The Institute of Medicine (IOM) has recently called for dramatic changes in the conduct and funding of National Cancer Institute studies. One of the key recommendations of this report is to focus on innovation in clinical trials. This implies the need to move on to alternative strategies when a well-designed trial shows a negative result, such as here. One potential solution to this issue may be found in the IOM...
recommendation that “only well-designed clinical trials that have the greatest possibility of improving survival and quality of life for cancer patients are undertaken.” Native American tribal wisdom says that when you discover you are riding a dead horse, the best strategy is to dismount. Based on a large amount of animal work, and an initial positive clinical trial, P-gp inhibition held significant promise to improve survival in AML, especially in the elderly. However, based on the findings of this study, combined with the previous trials, further clinical trials in this area should be viewed with skepticism, and effort redirected to other, more novel, strategies.

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REFERENCES

Comment on Wölfler et al, page 4116

Tracing C/EBPα+ cells and their progeny

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In this issue of Blood, Wölfler and colleagues describe a mouse model that allows tracking of hematopoietic cells that express C/EBPα and the progeny thereof. Their data indicate that expression of C/EBPα drives commitment of multipotent progenitors toward a myeloid cell fate, but lymphoid potential is retained as well.

Multipotent hematopoietic stem cells (HSCs) that reside in the bone marrow can give rise to all myeloid and lymphoid lineages of the blood, but the process of lineage specification is complex. Cytokines and growth factors are critically important, although there is still lively debate about the “instructive” versus “permissive” nature of their actions (see comment in Enver and Jacobsen1). Cytokines are able to instruct progenitor cells to develop into a certain lineage,2 but stem cell–intrinsic programs that predetermine lineage fate appear to exist as well (reviewed in Schroeder3). Both these extrinsic and intrinsic cues will ultimately lead to changes in gene expression programs that will guide the differentiation of progenitors into mature cell types, and the activation of transcription factors is key to these processes.

One such transcription factor is the CCAAT/enhancer-binding protein α (C/EBPα). It has been demonstrated that C/EBPα is essential for the formation of granulocytes and in particular for the transition from the common myeloid progenitor (CMP) toward the granulocyte/monocyte progenitor (GMP).4 Initial studies suggested that C/EBPα is expressed at low levels in HSCs, is up-regulated upon maturation toward CMPs and GMPs, and is not expressed
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