pies. Of the 74 patients, 18 (24%) achieved complete remission (CR) and 2 nodular partial response, and 28 partial response. The OR was 65%. In another randomized phase 2 study, Hillmen et al. compared an FCM (fludarabine + cyclophosphamide + mitoxantrone) regimen with FCM plus rituximab in previously treated CLL. In this study, a 4-drug regimen induced a higher CR and CR(i) rate (43%) than FCM alone (13%) (see figure). However, the study design did not allow for a statistical comparison of the 2 combinations.

In conclusion, despite the significant progress made in recent years, available therapies for refractory/refractory CLL are only partially effective, and there is an obvious need to develop better strategies and new, more specific and active drugs.

Conflict-of-interest disclosure: The author received research grants from Hoffman-LaRoche and Biogen Idec, and serves as a consultant with Hoffman-LaRoche and Biogen Idec.

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Every cloud has a silver lining

Comment on Lewandowski et al, page 443

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In this issue of Blood, Lewandowski and colleagues show that elevated extracellular ROS in the bone marrow are not just one of the signs of the damage induced by high doses of irradiation, but actually lead to up-regulation of VCAM-1 on endothelial cells, therefore mediating transplanted HSC homing and initial proliferation.1

Reactive oxygen species (ROS) are used to our advantage by immune cells, which release them in bursts as a lethal weapon against a number of pathogens, but otherwise they tend to play the role of the bad guys in most stem cell studies. Side products of each cell’s respiratory chain, they inevitably accumulate as a result of active metabolism. As they generate several types of damage at the protein, lipid, and DNA levels, ROS take on a role that is both double-edged and highly aggressive. But what do they do to our advantage? ROS can have a positive effect? The answer is yes.

In recent years, 4 drug combination therapies have been developed for the treatment of chronic lymphocytic leukemia (CLL). The combination of fludarabine, cyclophosphamide, and rituximab (FCR) has been shown to be superior to FCR alone in terms of response rate, progression-free survival, and overall survival.2

However, the results were less impressive than those reported in the present study of Byrd et al.2 The FCAR (FCR + alemtuzumab) immunotherapy regimen was evaluated in heavily pretreated patients with up to 14 previous therapies.3 Of the 74 patients, 18 (24%) achieved CR, 2 nodular partial response, and 28 partial response. The OR was 65%. In another randomized phase 2 study, Hillmen et al. compared an FCM (fludarabine + cyclophosphamide + mitoxantrone) regimen with FCM plus rituximab in previously treated CLL. In this study, a 4-drug regimen induced a higher CR and CR(i) rate (43%) than FCM alone (13%) (see figure). However, the study design did not allow for a statistical comparison of the 2 combinations.

In conclusion, despite the significant progress made in recent years, available therapies for refractory/refractory CLL are only partially effective, and there is an obvious need to develop better strategies and new, more specific and active drugs.

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Oxidative stress on VWF proteolysis

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In this issue of Blood, Chen and colleagues demonstrate that the rate of cleaving VWF by ADAMTS13 is significantly slowed when the residue Met^{1606} in the VWF A2 domain is oxidized.\(^1\) The finding adds a new dimension to the complexity of regulating VWF cleavage and links the rate of VWF proteolysis to the state of oxidative stress.

Von Willebrand factor (VWF) multimers secreted from Weibel-Palade bodies of endothelial cells are enriched in ultra-large forms that are rapidly cleaved by the zinc metalloprotease ADAMTS13. Enzyme deficiency is associated with the development of thrombotic thrombocytopenic purpura as well as with conditions associated with systemic inflammation. There have been extensive studies on how VWF proteolysis is initiated and regulated, mostly focusing on identifying the interface between the substrate and metalloprotease, and specific mutations that alter the rate of cleavage. The current study has delineated a new regulatory mechanism. The study found that Met^{1606}, within the peptide bond (Tyr^{1605}–Met^{1606}) targeted by ADAMTS13, is oxidized to the sulfoxide by hypochlorous acid (HOCl) in vitro. The oxidative modification significantly slows the rate of cleaving an isolate A2 domain and purified VWF multimers by the metalloprotease. The study is significant because it provides the first experimental evidence that VWF proteolysis could be regulated by oxidative stress, which results from accumulation of reactive oxygen species including HOCl.\(^2\) The study is also provocative because it raises several interesting and important questions. First, is Met^{1606} the only amino acid in VWF multimers that is subjected to oxidative modification? The answer is likely to be no, even though the current study is focused on the HOCl modification of a specific methionine residue. VWF contains a high percentage of cysteine residues (8.3%), some of which are in thiol forms that could be sensitive to regulations by redox in general and HOCl in particular. Consistent with the notion, an early report has shown that thiol(s) in the VWF A3 domain is targeted by a redox-sensitive activity associated with thrombospondin-1.\(^3\)

The question remains as to whether different reactive oxygen species differentially modify specific amino acids within a VWF multimer, leading to different functional outcomes. Second, does oxidation also affect VWF adhesion activity? The answer is likely to be yes. There is no direct evidence as to whether VWF with oxidized Met^{1606} is more or less adhesive, but converting thiols in VWF multimers to disulfide bonds is associated with enhanced VWF binding to platelets.\(^4\) Third, is VWF oxidation by reactive oxygen species permanent or transient? A disulfide bond is traditionally considered to be a permanent basic posttranslational modification critical for maintaining the tertiary structure of a given protein. However, increasing evidence also suggests that the oxidative modification occurs extracellularly to nonstructural thiols in response to changes in a redox environment.\(^5\) The blood redox system is composed of proteins and small-molecule thiols, and its balance can be changed in a variety of (patho)physiologic conditions. One well-known example is that the plasma redox potential is approximately 13 to 1 as measured by the ratio of reduced to oxidized glutathione.\(^6\) However, this reducing state can be made transiently oxidizing in conditions such as oxidative stress. The question is whether the oxidative modification to VWF is reversible when the environment returns to a reducing state. Demonstrating such reversibility will answer a fundamental question as to...
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