Rituximab in autoimmune cytopenias: for which patients?

The anti-CD20 monoclonal antibody rituximab represents a new tool for treating B-cell malignancies, especially low-grade lymphomas. More recently, the drug has been shown to be helpful in some patients with refractory autoimmune cytopenias, and the papers by Zaja et al.1 and Delgado et al.2 in this issue of Haematologica extend our knowledge on these new, emerging indications. The most convincing evidence of benefit from rituximab in this setting has been reported for patients with cold agglutinin disease. This uncommon hemolytic anemia, often associated with a chronic lymphoproliferative disease, is poorly responsive to steroids, cytotoxic chemotherapy or other therapeutic approaches. A favorable outcome, however, was observed in 12 of 14 patients (85%) given rituximab in a small prospective study3 and in some case reports.4-7 Three patients were previously untreated, whereas the others had failed several lines of conventional therapy. The results of rituximab treatment in patients with refractory warm-antibody autoimmune hemolytic anemia are less encouraging. Only a few case reports are available8-10 and a complete hematologic remission has been achieved in about 50% of patients. In one study, anemia was reported to worsen after rituximab administration.10 As far as concerns rituximab in chronic autoimmune thrombocytopenia, one cohort study on 25 patients has been published in full11 and three other prospective series of more than 10 patients each have been reported in abstract or preliminary form.12-14 Overall, a sustained increase of platelet count was achieved in 28% to 54% of patients resistant to previous treatments. Most investigators agreed that this drug should be carefully considered in severely thrombocytopenic patients who do not respond to standard therapy. The successful use of rituximab has also been reported in patients with pure red cell aplasia6 and autoimmune thrombocytopenia and neutropenia,15 refractory to conventional therapy.

The benefit of rituximab should be weighed against its potential risks. The drug is generally well tolerated, but a life-threatening syndrome of bronchospasm and/or hypotension has been described in about 10% of patients treated for lymphoma, particularly during the first infusion.16 The syndrome is due to massive cytokine release from neoplastic cells and is more severe in patients with a high tumor burden and/or circulating tumor cells above 50,000/mL. Another side effect of the drug is the long-lasting impairment of humoral immunity, leading to an increased risk of viral and bacterial infections. Pure red cell aplasia due to parvovirus B19,17 re-activation of acute hepatitis B,18 and bilateral bacterial pneumonia19 have been reported after rituximab treatment. In occasional patients, the drug has also been associated with induction or exacerbation of autoimmune diseases, including acute agranulocytosis20 and lupus thrombocytopenia.21 (Editorial note. The following paper on the use of rituximab recently appeared in this journal.22-29)

Balancing benefits and risks, the possible indications for the use of rituximab in autoimmune cytopenias are summarized in Table 1. Clearly, there is urgent need for further studies. The optimal schedule of administration of the drug and the duration of the clinical effect are important issues to be addressed. Most importantly, larger, prospective series of patients consecutively treated are required to avoid the bias of preferentially reporting successful cases. Ideally, all patients given rituximab for these and other still uncertain indications should be registered and evaluated.

Table 1. Possible indications for the use of rituximab in autoimmune cytopenias.

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<th>Indications</th>
<th>Evidence</th>
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<td>Patients with cold agglutinin disease, requiring treatment (ie. transfusion-dependent anemia and/or disease-related symptoms), also as first-line therapy (standard therapy usually ineffective)</td>
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<tr>
<td>Patients with high immune thrombocytopenic purpura, requiring treatment (ie. platelet count &lt;10,000/mL and/or bleeding symptoms) and refractory to standard therapy</td>
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<tr>
<td>Patients with warm-antibody autoimmune hemolytic anemia, pure red cell aplasia or immune thrombocytopenia and neutropenia, with severe disease requiring treatment and refractory to standard therapy*</td>
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Standard therapy includes full-doses steroids, high-doses i.v. immunoglobulins, splenectomy and immunosuppressive drugs. * Evidence of benefit still limited in these indications. See text for details.
reach this goal, a project of clinical epidemiology and surveillance of rituximab use has recently been launched and will be operative in all Italian hospitals very soon.

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References

Novel genes, proteins, and inherited disorders of iron overload: iron metabolism is less boring than thought

Until a few years ago, only three proteins of iron metabolism were known: transferrin, transferrin receptor and ferritin. From a clinical point of view, a step forward was the observation that both ferritin and transferrin receptor have soluble forms. The level of serum ferritin parallels the concentration of storage iron within the body, regardless of the cell type in which it is stored, so that determining serum ferritin levels represents a very convenient means of assessing iron balance in clinical practice. The soluble transferrin receptor assay is much less employed in clinical settings, despite the fact that its determination is a convenient way of assessing erythropoietic activity.

Of central importance to our understanding of iron metabolism was the later discovery that cellular iron homeostasis in mammalian cells is maintained by the co-ordinated regulation of transferrin receptor and ferritin synthesis that occurs at the translational level and is mediated by cytoplasmic mRNA-binding proteins, known as iron regulatory proteins (IRPs). These proteins are capable of sensing cellular iron status and of interacting with mRNA stem-loop structures known as iron-responsive elements (IREs). Mutations that cause disease through increased efficiency of mRNA translation have been discovered, allowing recognition of hereditary hyperferritinemia/cataract syndrome and defining translational pathophysiology as a novel mechanism of human disease.

Following the identification of HFE as the gene of HLA-related genetic hemochromatosis, homozygosity for the HFE C282Y mutation has been found in more than 90% of North European and more than 80% of American patients of European origin clinically diagnosed as having genetic hemochromatosis. However, markedly lower frequencies (50-64%) for C282Y homozygosity have been found in severely iron-loaded patients belonging to populations of Southern Europe. Additional HFE mutations have been reported, the most frequent one being the A193T mutation leading to the S65C missense substitution, while no conclusive evidence of abnormal gene expression in heterozygotes has been found. The precise function of the HFE protein in physiologically inhibiting iron absorption is not fully clear. The HLA-related hemochromatosis defined as hemochromatosis HFE (OMIM 235200).

The availability of molecular tools for studying HFE mutations has allowed investigators to identify novel forms of non-HFE related genetic hemochromatosis (GH). Fifteen years ago we described juvenile GH as a distinct nosological entity. Patients present with hypogonadotropic hypogonadism, and, unless proper treatment is started, die early because of cardiac dysfunction. In a collaborative study, the juvenile locus was later mapped to chromosome 1q. Juvenile genetic hemochromatosis is defined as hemochromatosis type 2, or HFE2 (OMIM 602390). This gene must play a crucial role in iron metabolism, perhaps acting as the erythropoietic regulator of iron absorption hypothesized by Clement Finch decades ago.

In a few Italian families with non-HFE related hereditary hemochromatosis, Camaschella et al. later found that affected individuals were homozygous for point mutations in the gene coding transferrin receptor 2 (TFR2), suggesting that this may represent the molecular basis for this familial iron overload syndrome. TFR2 is a member of the transferrin-like receptor family with unknown function, but characterized by a restricted pattern of expression in the liver. The TFR2 mutations responsible for hemochromatosis type 3, or HFE3 (OMIM 604250) appear to be private mutations.

In nearly simultaneous reports, a Dutch group recently described pedigrees with atypical hemochromatosis inherited as an autosomal dominant trait. The two groups found different missense mutations in the gene encoding the iron export protein ferroportin1 (also known as IREG1, or MTP1). This dominant type of genetic iron overload is defined as hemochromatosis type 4, or HFE4 (OMIM 606069). Ferroportin1 plays key roles in two different aspects of iron metabolism, absorption of dietary iron by duodenal enterocytes and release of iron from body stores by reticuloendothelial cells.

Nicolas et al. recently reported severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. Studies on genes that may account for the abnormalities of iron homeostasis in USF2(-/-) mice allowed the authors to identify hepcidin as the gene responsible for iron overload in these animals. This observation prompted Majore et al. to look for mutations in the hepcidin gene in Italian patients with non-HFE related GH. Their findings, reported in this issue, are negative, but this does not exclude that hepcidin may be involved in the pathogenesis of inherited iron overload in humans, and that HFEn will be discovered in the near future.
Although the most common GH at present is the HFE-related disorder in population of Northern European extract, physicians working in other regions of the world are facing a less boring reality. Heterogeneity is challenging in both biology and clinical medicine, but it is also stimulating, inducing investigators to pursue new ideas and allowing science to progress.

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