

Advances in Hematology

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*Current Developments in the
Management of Hematologic Disorders*

Hydroxyurea and New Agents for the Treatment of Sickle Cell Disease

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Could you describe how the sickle cell gene works to cause sickle cell disease?

Normally, hemoglobin, a protein in red blood cells (RBCs), delivers oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. When the oxygen is delivered to tissues, the RBCs do not undergo any change and the hemoglobin maintains its structure.

In the case of sickle cell hemoglobin, there is a tendency for the hemoglobin molecules to aggregate and form long rods within the RBC once the oxygen has been delivered to tissues. These rods distort the shape of the cell, at the very extreme, causing them to sickle. These sickle cells are not able to pass through the small microvessels in the circulatory system, and thus obstruct blood flow. When blood flow is obstructed, oxygen cannot be delivered appropriately and the tissues become deprived of oxygen. In the absence of oxygen, tissues begin to die, and ultimately, organ function will be diminished. The cumulative effect of malfunctioning organs is diminished life expectancy.

Therefore, sickle cell disease is a chronic process that is cumulative in nature, punctuated by acute events in which there is a severe occlusion of flow to certain areas of the body, notably the bone.

How does hydroxyurea, the standard agent for treating sickle cell disease, work?

Hydroxyurea (HU) is approved by the US Food and Drug Administration for the treatment of adults with moderate-to-severe sickle cell disease, defined by having complications of the disease, particularly acute episodes of sickle cell crisis pain.

HU treats the chronic vaso-obliterative processes of sickle cell disease, thereby eliminating the intensity and duration of the acute problems. HU works by switching on fetal hemoglobin (HbF), which is present in the bloodstream of a developing fetus during the second or third trimesters of life. HbF is able to interfere with the effect of the sickle

hemoglobin by disrupting the rods of hemoglobin inside the RBCs, thus restoring the cells to their normal shape. There are other potential avenues by which HU works, but this is the principal mechanism.

In responding patients, quality of life is improved, with many patients being able to return to work, enjoy normal exercise capacity, and satisfactorily engage in other activities of daily life. This agent represents a major breakthrough in the treatment of sickle cell disease; prior to its development, therapy was directed at treating the complications as they arose, as opposed to preventing the complications from developing.

What are the other potential pathways by which HU works?

HU has been used for decades for the treatment of certain preleukemic conditions, the so-called myeloproliferative diseases. In those conditions, the RBCs, white blood cells (WBCs), or platelets are increased in number. In this setting, HU lowers the number of cells, and is particularly effective when it is the WBCs or platelets that are increased. As would be expected, HU also lowers WBC and platelet counts in sickle cell disease, although to a lesser extent at the dosages commonly prescribed. Because WBCs may have an untoward effect in terms of blood circulation in patients with sickle cell disease, HU has a beneficial effect in this setting.

Why was HU developed for the treatment of sickle cell disease rather than other chemotherapeutic agents?

The application of HU in sickle cell disease was the result of the observation that many agents in the class of cytotoxic drugs, which includes agents such as azacitidine, cytosine arabinoside, and cyclophosphamide, have the capability to stimulate HbF synthesis. However, the other agents in this class are usually administered intravenously (IV) and given for short courses to patients with leukemic and other conditions. These agents may cause chromosomal damage and can lead themselves to the development of certain types of cancer. HU was selected from among these agents for devel-

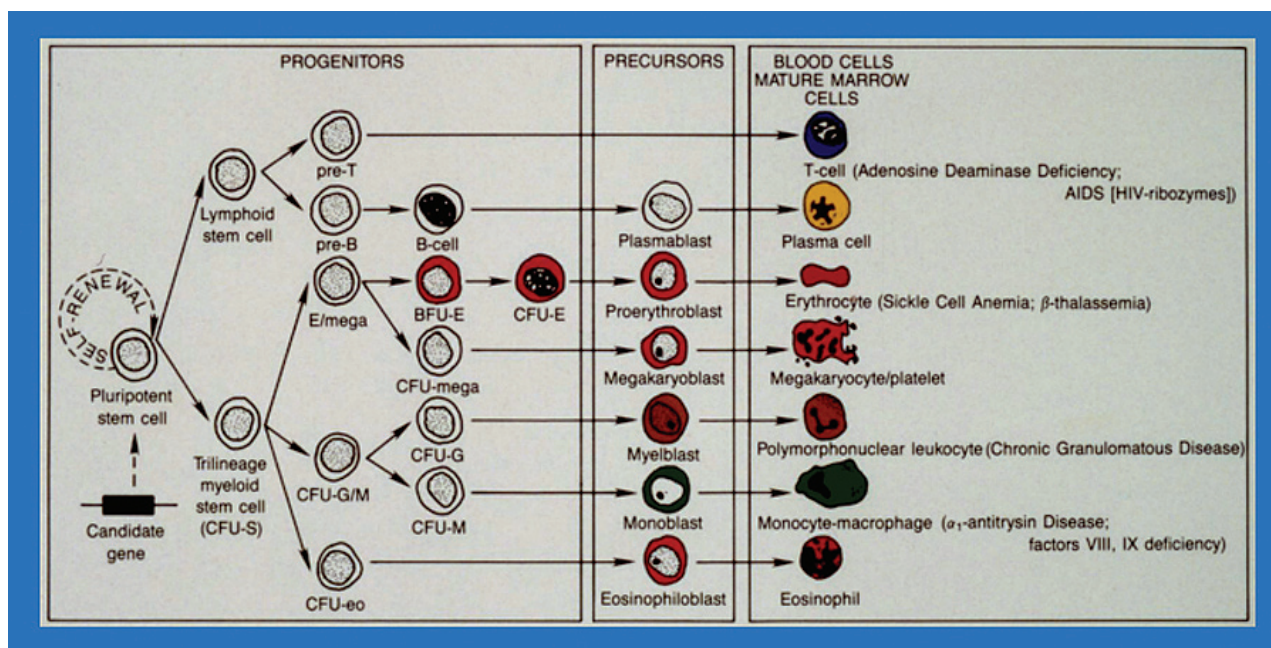


Figure 1. Application of gene therapy to blood diseases.

opment in treating sickle cell disease because it also stimulates HbF and appears to be the safest, with a more limited tendency to cause either carcinogenesis or leukemogenesis.

In addition, HU can be administered orally. The dose can be easily titrated up or down in order to induce HbF and lower the WBC in a controlled manner. The therapeutic window is also much larger with HU than with some of the IV medications.

Does HU cure sickle cell disease, or does the disease return once treatment is stopped?

HU has a fairly limited effect on developing bone marrow cells because it has a fairly short half-life. After treatment is stopped, the beneficial effects will diminish over time and the patient will return to their condition prior to treatment. Therefore, the drug needs to be administered on a chronic basis.

Do all patients respond to HU therapy?

No. Only approximately 70% of patients experience a clinical response to HU, manifested by a substantial increase in HbF. Among those patients who do respond, there is a great heterogeneity in the degree to which HbF levels are increased; some patients respond extremely well, some respond moderately well, and in some, results are not very robust. In actuality, approximately 50% of patients with sickle cell disease respond both hematologically and clinically. Sickle cell disease in the other 50% of patients remains undiminished from HU therapy.

In addition, while HU therapy diminishes symptoms in patients with sickle cell disease, complications do still occur, albeit in a less severe manner. Therefore, HU represents an advance in the treatment of sickle cell disease, but not a cure.

What would constitute a cure of sickle cell disease?

Curing sickle cell disease would involve somehow replacing the defective sickle gene by substituting a normal gene, or at least to position a normal gene to take over the function of the abnormal sickle genes. Gene therapy researchers are exploring this approach.

How is this strategy being pursued in research?

For sickle cell disease, the essential elements of gene therapy have been available for quite some time (Figure 1). The first component of gene therapy is to know the defective gene. The defective gene in sickle cell disease and thalassemia, a related disorder, was among the first to be cloned and chromosomally localized. The results of basic and clinical research have suggested ways to compensate or correct these genes. It is possible that inserting a normal beta-globin gene or HbF gene could compensate for the effects of the sickle gene or potentially replace that gene completely.

The second component of gene therapy is having the specific stem cell—in this case, hematopoietic stem cells—in which to introduce the corrective genes. For blood diseases, this component includes the bone marrow or peripheral blood stem cell. The technology to do effective bone marrow transplants has been available for several decades. What is not yet available is an effective method for identifying and expanding those stem cells in a manner that would allow one replacement to be sufficient.

Finally, the physical manner in which the corrective genes are introduced into cells has generally relied on viral vectors, including retroviruses, adeno-associated viruses, and others. However, these vectors have their own attendant risks.

Right now, a great deal of research is aimed at isolating and expanding the hematopoietic or bone marrow stem cells and

also developing better delivery systems to keep the corrective gene in place. It is hoped that effective gene therapy for sickle cell disease will be available within the decade.

What other HbF-inducing approaches are being explored for the treatment of sickle cell disease?

With respect to HbF, there are a number of approaches being evaluated. The small-chain fatty acid class of drugs, of which butyrate is the parent compound, may be effective in this setting. Compounds from this class of agents have been shown to be effective in inducing HbF in animal models and cell cultures, either alone or in combination, and appear to have an additive effect in inducing HbF in patients with sickle cell disease.

Cytokines, including erythropoietin, appear to work alone or in combination with HU or other cytotoxic drugs to further stimulate or augment the expression of HbF. Studies are moving forward in this area.

Are other avenues of treatment being explored?

Yes. Polymerized sickle hemoglobin within the cells is associated with 2 major problems: on the one hand, it induces membranes to activate pumps abnormally, thereby causing cells to become dehydrated, and on the other hand, to be removed rapidly from the cells, leading the bone marrow to produce a greater number of new cells to compensate for that loss. The new cells tend to be sticky and adhere to the endothelium very readily.

Two nonoverlapping approaches work along these pathways. The first strategy is to use drugs that can restore the normal anion and cation levels inside the cells and keep them well hydrated. A class of drugs, the parent compound of which is chlortrimazole, an antifungal agent, has been shown to accomplish this in cell culture and animal model studies. Certain magnesium salts also appear to correct particular abnormal channel defects that are induced in sickle cells.

Antiadhesive agents are also being developed. Researchers are regularly identifying new adhesion molecules that appear to be overexpressed in sickle cells in comparison with normal RBCs. Even if cells are not sickled, they may have the ability to stick to the lining of vessels, thus obstructing blood flow.

Another treatment pathway involves the recognition that when RBCs are destroyed in the circulation, they liberate free hemoglobin into the bloodstream. This free hemoglobin can bind nitric oxide, a very potent vasodilator. This binding can cause problems in circulatory flow. Several groups are attempting to augment the endogenous level of nitric oxide in order to counteract the effect of the free hemoglobin. The class of drugs to which sildenafil (Viagra, Pfizer) belongs changes the levels of endogenous nitric oxide as its principal mode of action.

How are transplants being pursued for the treatment of sickle cell disease?

Theoretically, any genetic disease affecting the bone marrow can be cured if the patient has a suitable donor. However, it is estimated that less than 25% of patients with sickle cell disease have a matched donor. Clinical experience has shown that the optimal time for a patient to undergo a transplant is during early childhood or adolescence, because they will not have suffered the cumulative effects of sickle cell disease on their lungs, liver, heart, and other organs. However, the severe complications of sickle cell disease manifest to different degrees and at different times; an individual may experience crises once or twice per year, or patients may reach their young adulthood or middle age years without experiencing severe acute complications, making the selection of appropriate patients for transplants at times problematic. When end-organ damage develops, extensive myeloablation with radiation and chemotherapy given as a pretransplantation conditioning regimen in this setting may be too toxic.

Several groups are exploring the use of mini-transplants, or nonmyeloablative approaches, which do not involve high-dose chemotherapy or radiation therapy. It may be that not all of the marrow needs to be obliterated; if the marrow can be reduced sufficiently to create spaces in which the “donor” cells can reside, the 2 cell populations can coexist, a state known as mixed chimerism. Mini-transplants have shown efficacy in treating some solid and non-solid malignancies and are now being evaluated in the treatment of sickle cell disease, with promising preliminary results. Many adult patients who do not respond to treatment with HU now have an opportunity to mollify their disease. As we learn more about how to maintain a mixed chimerism environment in the bone marrow, we will also gain understanding about sickle cell disease that will likely inform the development of gene therapy, so that we can eventually cure this condition.

Suggested reading

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