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Interfering with leukemic stem cells

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Abstract

Kinase inhibitors such as imatinib (Gleevec) have improved the outlook for many patients with chronic myeloid leukemia and related blood disorders. But such drugs fail to target the leukemia stem cell population and may not be curative. Krause and Van Etten discuss several clinical studies that suggest that interferon- α may provide a solution by selectively eliminating leukemic stem cells—although only more basic research will tell us whether this is true and how it may happen.

Recombinant interferon-alpha (IFN- α), an immunomodulatory cytokine, is used to treat chronic hepatitis C virus infection and as a therapy for several cancers, such as melanoma and Kaposi's sarcoma. IFN- α also has potent therapeutic activity in the myeloproliferative diseases (MPDs), such as chronic myeloid leukemia (CML), polycythemia vera, and essential thrombocythemia. MPDs are clonal hematopoietic stem cell disorders characterized by overproduction of mature myeloid or erythroid cells, which share a common pathophysiology involving dysregulated tyrosine kinase signaling¹.

Despite the effectiveness of IFN- α , its mechanism of action in the MPDs is poorly understood. Interest in the topic is now rekindled by several recent clinical studies^{2–5} that hint that IFN- α may target leukemic stem cells.

Clinicians of a certain age will recall when medical therapy of CML was palliative. Busulfan or hydroxyurea, once the drugs of choice, suppressed production of myeloid cells but did not selectively target the malignant clone containing the Philadelphia chromosome, the CML-specific translocation product that creates the *BCR-ABL* fusion gene. Nor did these drugs interrupt the inexorable progression of CML from chronic phase, in which myeloid differentiation is preserved, to blast crisis, a terminal condition resembling acute leukemia.

In 1986, IFN- α was tested in CML patients and found to induce cytogenetic and even molecular remissions in which *BCR-ABL* mRNA transcripts became undetectable. In some subjects, these remissions were maintained when treatment was discontinued⁶. IFN- α was also found to normalize blood counts in people with other MPDs, including some subjects with polycythemia vera and essential thrombocythemia⁷. Cytogenetic studies of selected subjects suggested that IFN could specifically suppress malignant stem cells in MPDs that lack a Ph chromosome, but it was impossible to prove such effects in the absence of a broadly applicable molecular marker.

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In 1990, the demonstration that the product of the Philadelphia chromosome, the BCR-ABL fusion tyrosine kinase, could induce CML-like disease in mice accelerated the search for drugs that could block its enzymatic activity¹. In 2001, the ABL kinase inhibitor imatinib mesylate abruptly supplanted IFN- α as front-line therapy for patients newly diagnosed with CML. Treatment with imatinib results in vastly superior cytogenetic and molecular responses⁸, but imatinib and other second-line ABL kinase inhibitors are plagued by the problem of acquired resistance and their inability to eliminate quiescent BCR-ABL⁺ stem and progenitor cells. These drawbacks have revived the search for treatment strategies that can eradicate leukemic stem cells in CML and other MPDs⁹.

In 2005, the discovery of a somatic mutation (V617F) in the JAK2 tyrosine kinase in nearly every patient with polycythemia vera and about half of patients with essential thrombocythemia¹⁰ provided a molecular marker for these diseases that was analogous to BCR-ABL in CML. With this marker in hand, researchers have provided clinical evidence suggesting that IFN- α may specifically target leukemic stem cells in these MPDs.

In a study published in *Blood*, Kiladjian *et al.*² treated a cohort of polycythemia vera patients with a pegylated formulation of IFN- α -2a. They observed complete hematological remission (normalization of erythrocyte and leukocyte counts) in 83% of subjects. In 24 of 27 evaluable subjects, remission was accompanied by a decrease in the mutant *JAK2* allele in granulocytes from a mean of 49% to 27%², and in one subject, the mutant *JAK2* became undetectable, consistent with a molecular remission. Similar results have been obtained in an ongoing study by Quintás-Cardama *et al.*³ examining PEG-IFN- α -2a treatment in individuals with polycythemia vera and essential thrombocythemia.

A third report described 12 patients with CML who achieved molecular remission on imatinib, and who subsequently discontinued kinase inhibitor therapy⁴. Half the patients promptly relapsed with detectable *BCR-ABL* mRNA transcripts, while the others remained in molecular remission without imatinib, with a median follow-up of 18 months. Interestingly, all six of the latter patients had been previously treated with IFN- α ⁴. Another recent study found that imatinib can induce molecular remission in more than half of patients who have prior cytogenetic remissions in response to IFN- α ⁵, a much higher rate than in subjects with CML that had not been previously treated with IFN- α ⁸.

Collectively, these studies provide strong but indirect evidence that IFN- α preferentially targets the mutant clone in CML, polycythemia vera and essential thrombocythemia and might act to decrease or eliminate the malignant stem cell population in these MPDs.

The relative kinetics of the molecular responses to imatinib and IFN- α in CML also support this hypothesis. *BCR-ABL* mRNA transcripts show an initial rapid decline in imatinib-treated patients that may be the result of elimination of committed progenitors. This decline is followed by a plateau – reflecting resistant leukemic stem cells¹¹, whereas molecular responses in IFN-treated CML patients require much longer treatment periods⁶. The fact that IFN- α can induce molecular responses in both CML and polycythemia vera further suggests that leukemic stem cells expressing dysregulated TKs might be uniquely sensitive to this cytokine.

These clinical “bedside” findings argue for additional basic and translational “bench” research into the molecular mechanisms of IFN action in the MPDs. Twenty years after the introduction of IFN therapy for MPD, little is known about how it operates, nor why some patients respond while others do not.

The possibilities are numerous: some actions of IFN may work directly on the malignant stem cell, such as induction of interferon regulatory factor-8 (ref. ¹²) and Fas, and inhibition

of *BCR-ABL* transcription¹³. IFN- α also selectively impairs proliferation of primitive CML progenitors¹⁴. Moreover, both *BCR-ABL* and *JAK2 V617F* promote hematopoietic cell proliferation and survival through pathways involving the cell cycle regulator p27 and Foxo transcription factors – providing a potential common mechanism for IFN. In addition to direct effects, IFN- α may also target malignant stem cells through its ability to restore normal β_1 -integrin-mediated adhesion to the bone marrow niche. IFN- α also has pleiotropic immunological actions, including increasing the cytotoxicity of T- and NK cells, and inducing cell-mediated and humoral immune responses to candidate MPD antigens¹⁵.

More work at the bench may illuminate the basic mechanisms of IFN- α in CML and polycythemia vera and thereby offer new approaches to eradicate malignant stem cells in the MPDs, resulting in permanent cure. On the clinical side, randomized studies of IFN- α in combination with kinase inhibitors and with vaccination are warranted in people with CML who have not attained molecular remission on imatinib.

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