Chronic Myelogenous Leukemia: Update on Biology and Treatment

By Ellin Berman, MD [5]

Chronic myelogenous leukemia (CML) is an intriguing disease for reasons that point to important biological differences between this and other types of leukemia:

1. Routine chemotherapy with either busulfan (Myleran) or hydroxyurea (Hydrea) has been superseded by interferon-alfa (Intron A, Roferon-A), a compound with effects that may not be limited to direct cytotoxicity.

2. Relapsed disease in the post-allograft setting can be eradicated by either interferon or the infusion of donor leukocytes.

3. Disease progression is frequently linked to accumulation of well-characterized chromosomal abnormalities in addition to the Philadelphia chromosome.

The M. D. Anderson group is responsible for the first observation, has been instrumental in dissecting the cells responsible for the graft-vs-leukemia (GVL) effect noted in the second, and has been among the leaders in devising novel technologies to detect the chromosomal abnormalities mentioned in the third. It is therefore only natural that members of this group should provide a timely update on this disease.

New Insights About Interferon

Since Talpaz et al published the original CML interferon study in 1983,[1] several features regarding its use have become clear. First, interferon appears to be most active when begun early (within the first 6 months) after diagnosis. Also, interferon appears to be most effective at doses in the range of 5 MU/m²; however, responses can be seen at lower doses.

Although initially interferon was thought to be inactive in patients with more advanced disease (ie, accelerated or blastic phase), a recent report from the M. D. Anderson group has found that it is active in patients who have accelerated disease, as manifested by clonal cytogenetic evolution.[2] Unfortunately, the authors do not discuss the potential mechanisms of interferon in this disease. Members of the M. D. Anderson group have been among the first to describe interferon-inducible genes and have studied the differences in gene expression between patients who have and have not responded to interferon. A hypothesis concerning the agent’s possible function would have been pertinent.

Interferon in Combination Regimens

O’Brien et al have now taken interferon one step further and have combined it both with standard chemotherapy, in the form of cytarabine (Ara-C), and with the plant alkaloid homoharringtonine (HHT), a drug that has shown activity in patients with late chronic phase CML. As mentioned in the review, both of these combinations appear to be quite active, perhaps more so than interferon alone. Preliminary data suggest that the time to cytogenetic response in the combination trials is shorter than the 9 to 12 months typically seen in patients treated with interferon alone.[Susan O’Brien, personal communication, 1998]
This would be an important factor for patients in whom a standard allogeneic bone marrow transplant carries a high risk of transplant-related mortality; in these patients, an initial trial of interferon might be warranted. While the treatment algorithm might be the same (ie, if no major cytogenetic response can be documented, bone marrow transplantation might be undertaken), the time frame for such a decision might be shifted significantly.

Bone Marrow Transplantation in CML

Bone marrow transplantation is curative for a significant proportion of patients with CML. It is clear from a number of studies that patients do best when transplanted in chronic phase; patients with accelerated or blastic phase have survival rates that approach 10% to 15%.

Too briefly mentioned in this review is the controversy regarding prior treatment with interferon in patients who undergo transplantation. Although it is true that the International Bone Marrow Transplant Registry (IBMTR) data did not show that prior treatment with interferon was a predictive factor,[3] both a large German series[4] and a recently reported series from Seattle[5] have shown the opposite.

Because the median age of patients with CML is about 50 years, T-cell depletion strategies were introduced in an attempt to decrease the incidence of graft-vs-host disease (GVHD) in this older population. Although this approach initially appeared to be successful, it proved to be at the expense of the GVL effect; the relapse rate after this form of transplant is significantly increased compared to the rate after a conventional transplant.

Kolb et al were the first to demonstrate that patients who have relapsed disease in the post-transplant setting could achieve a second remission with interferon combined with an infusion of donor lymphocytes.[6] This seminal observation has enhanced our understanding of the mechanisms involved in T-cell cytotoxicity and has proved an invaluable tool for the clinician.

In this regard, Mackinnon et al[7] published the results from our own center, which showed that the GVL effect could be observed at low doses of donor lymphocytes and that many of the responding patients had either no or minimal GVHD. Giralt, Champlin, et al[8] have further defined the T-cell subsets thought to be responsible for the GVL effect. This group has shown that CD8-depleted donor lymphocytes can induce cytogenetic remissions with a low rate of GVHD, and suggest that CD8+ lymphocytes are important effectors of GVHD but may not be essential for GVL.

Major clinical advances in the treatment of CML have come from clinical observations made by investigators. Thanks to these observations, the treatment of CML has evolved from standard chemotherapy to an approach that involves biological therapy and T-cell manipulation. Investigators at M. D. Anderson have been leaders in this field and are to be congratulated for maintaining their extensive database, perhaps the largest single-institution database of patients with this disease in the world. Perhaps more importantly, they are to be commended for keeping an open mind.

References:


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