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How close are we to curing chronic lymphocytic leukemia?

A common introductory statement in discussants of chronic lymphocytic leukemia (CLL) is that it is an indolent disease of older people which is presently "incurable." At the present time, the question has to be raised as to whether any patients with CLL are being cured. Over the years many hematologic malignancies have been transformed from devastating and uniformly fatal to routinely curable, such as childhood ALL and acute promyelocytic leukemia. The definition of cure is important. Many patients who die of other conditions when in complete remission of their malignancy can be classified as being cured. This may be the situation with CLL.

Considerable advances have been made in the treatment of CLL over the last 25 years. The discovery of purine analogs and combining these with alkylating agents and monoclonal antibodies such as rituximab and alemtuzumab have led to a dramatic improvement in the complete remission rate. In our own experience, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) has led to a 72% complete remission rate with the median remission duration being seven years for the CRs and a similar time for nodular partial remissions. From this predictor of the patients likely to stay in complete remission is the mutation status of their immunoglobulin heavy chain gene (IgVH). The unmutated groups of patients are all relapsing with a median remission duration of five years whereas 60% of the unmutated group is still in remission at eight to nine years. The cytogenetics of patients that relapse are dominated by 11q deletions on FISH or 17p.

These promising results are to be tempered with knowledge that most of these patients are under the age of 70 and our success rate in older patients is considerably less. The most important discriminator of long term outcome in patients over the age of 70 is the β_2-microglobulin with many of patients with lower values staying in long term remission. In addition, the patients in the M. D. Anderson Cancer Center studies do not have significant co-morbidities which limit applicability to a general patient population.

There is considerable interest in the use of alemtuzumab, rituximab and lenalidomide as post remission therapy to try and prolong remission duration. While this has been accomplished, there is no data at the present time to show that these remissions are sustained on a long term basis or that there is any survival advantage. It is clear that a number of

patients who have had allogeneic stem cell transplantation (SCT) are free of disease on a long term basis. It is obvious in relapsed patients after FCR, that many of these patients who have received allogeneic SCT are free of disease for considerable periods of time. The positive response to allogeneic SCT suggests that the cure of CLL will eventually be by immunologic mechanisms with immuno-sector cells being directed to the CLL clones specifically. It is clear that there has been a significant improvement in survival over the last 25 years. This is as a consequence of improved therapy and supportive care. We have the tools at our disposal to cure this disease as long as well have the patients and persistence to continue to address this challenging disorder.