

## CLINICAL HEMATOLOGY/ONCOLOGY NEWSLETTER

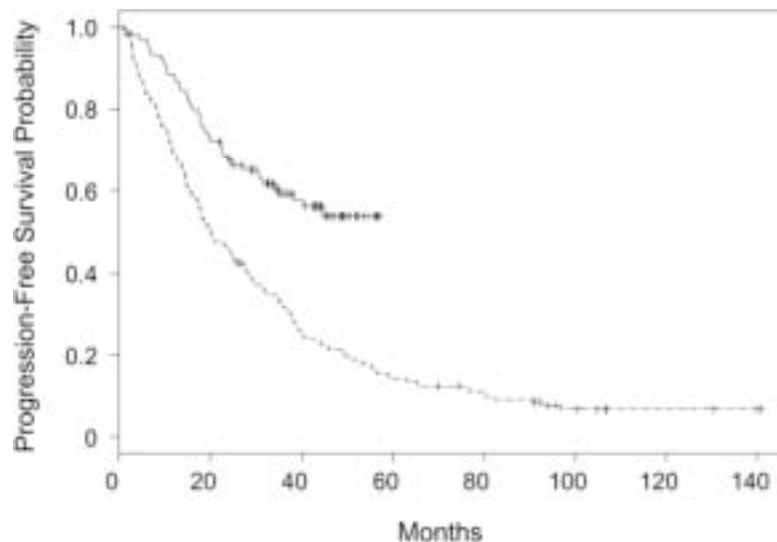
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### RE: "Progress at last!" in CLL; but, a few more years will tell!

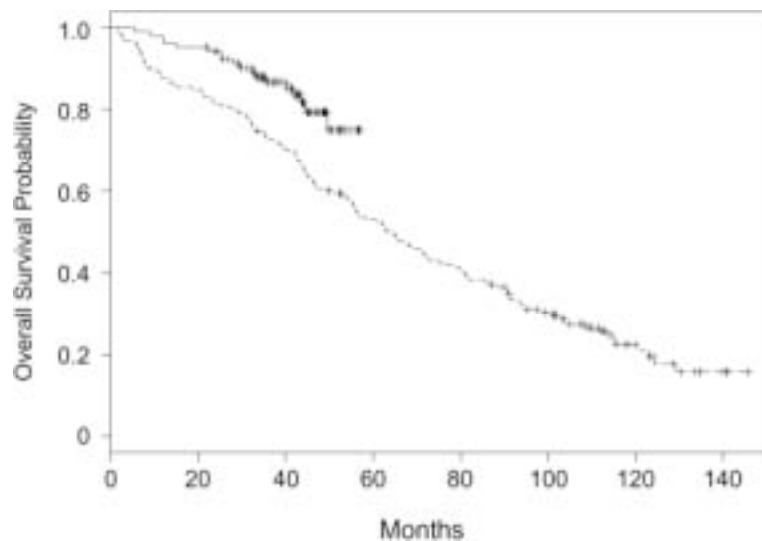
Several months ago, a note in *Blood* was entitled, "CLL therapy: progress at last!"[1]. The purpose of this month's Newsletter is to review those comments, as well as the article to which it refers, but look at the same data in a somewhat different light.

The commentator was editorializing on an article that reviewed the benefit of adding rituximab to fludarabine[2]. He noted that the purine analogs dramatically changed treatment approaches in this disease because of higher response rates and longer periods of time of remission as compared to alkylating agents. The article to which he was referring was a retrospective analysis of CALGB and US Intergroup studies in which rituximab was added to the purine analog, fludarabine. In this report, rituximab and fludarabine appeared to increase the progression free survival and overall survival in previously untreated CLL.



The graph shown above is taken from the manuscript and charts the progression free survival. The lower of the two curves represents the effects of treatment with fludarabine alone in a study that was started over 14 years ago and the upper curve reflects rituximab and fludarabine from a protocol that began 7 years ago.

The survival curves were also examined (see below).

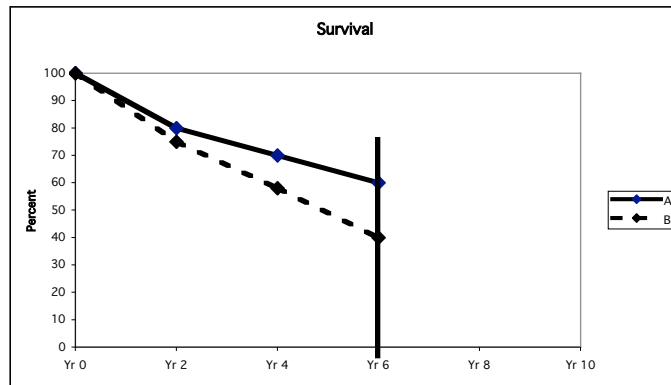


The earlier study included 178 subjects and the second study had only 104. The group that included the rituximab and fludarabine treatment was actually a combination of two different treatment arms and schedules, one with concomitant rituximab and the other sequential treatment. Additionally, these differences in the treatment schedule are confusing because some of the data represent 4 doses of rituximab while the other treatment arm had as many as 10-11 doses of the drug. The authors of the article were honest enough to point out these differences and they appropriately stated that the combined treatment of rituximab and fludarabine “may” improve overall survival as compared to fludarabine alone. However, the editorial writer indicates that there is “progress at last!”

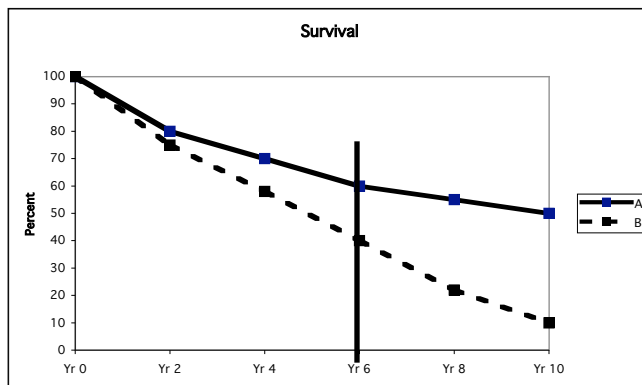
I am a fan and supporter of the use of rituximab in this disease and in many other disorders. Rituximab appears to make a difference for many patients, but a few words of caution! It is a giant leap from this data to assume that there is an improvement in overall survival. In aggressive malignancies, such as germ cell tumors, acute leukemia, Hodgkin’s, intermediate and high risk lymphomas, it is often true that the higher the response rate, the longer the progression free survival and overall survival. However, the nature of CLL and low-grade non-Hodgkin’s lymphoma is one of a treatable but incurable malignancy. We have gone from a single alkylating agent therapy initiated at the time of initial diagnosis to treatment of patients only when symptomatic because of a lack of improvement in overall survival. Furthermore, the results with single agent or multiple agent treatment make no differences in survival. Purine analogs provided a greater percentage in response rates and a longer period of time before relapse, but no obvious improvement in survival. When other agents such as alkylators were added to purine analogs, greater toxicity was noted. Furthermore, purine analogs alone are associated with a prolonged period of time (several months to a year) of severe immunosuppression; patients become T4 cell depleted. All of these facts have led many community oncologists to be apprehensive about purine analogs.

Certainly, if survival were to be improved, then the purine analogs would be used. However, to assume that rituximab and fludarabine improves survival based on these retrospective analyses of certain treatment arms of two different studies conducted 7 years apart is somewhat out of line with what we learned in Statistics 101.

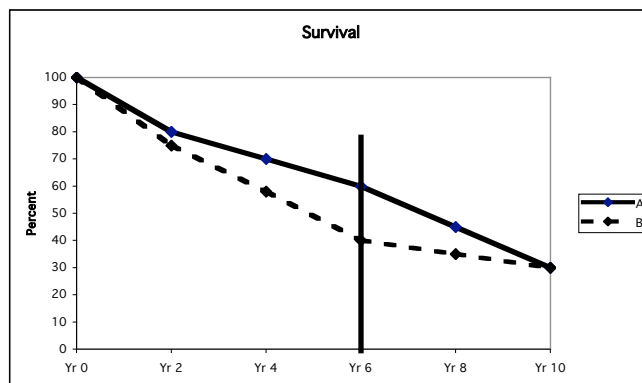
In CLL, looking at survival with 5 years of data is insufficient. As obvious examples, the curves below illustrate what may happen after 5 years. The data are not of CLL but only being artificially constructed.



Above is a graph of survival with Rx A and Rx B over 6 years. In the next graph, the next several years of observation confirmed the improvement seen with the first 6 years of Rx A.



But, in contrast, the next graph shows the survival curves eventually approaching one another; thereby indicating that Rx A caused only a delay in disease progression but without any improvement in survival. This phenomenon has been the track-record with CLL. Therefore, why put someone through additional toxicity for no overall survival



benefit.

There is “progress at last” but not so much from the combination of rituximab and fludarabine, but perhaps from the rituximab itself. It is a relatively well-tolerated drug that is effective, especially in the correctly selected CLL patient. It may actually work best at maintaining remissions. The non-selective chemotherapy treatments of the past acted as cellular toxins with no tumor specificities and no major achievements in survival. The older drugs provided treatment options to produce remissions when relapses had occurred. Rituximab (and other monoclonal antibodies) may focus on the cells of pathobiologic significance. More “progress” is needed with rituximab, predominantly to try to determine the correct frequency of administration and with what drug dosages.

References:

1. Montserrat, E., *CLL therapy: progress at last!* Blood, 2005. **105**(1): p. 2-3.
2. Byrd, J.C., et al., *Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011.* Blood, 2005. **105**(1): p. 49-53.