A close look at FCR

Although fludarabine, cyclophosphamide and rituximab (FCR) has long been standard treatment for CLL in America, there has hitherto been no evidence of its superiority to other treatments. While a large number of patients have been treated in an extended phase II trial at the MD Anderson Cancer Center in Houston, and the results of that study have been impressive, no randomized controlled trial data have been available. I am sure that this will be remedied at ASH this year since we know that the German trial comparing first-line FCR with FC has been completed, that at the first interim analysis it had met its primary endpoint, which was a significantly longer progression-free survival for one of the arms. It is possible, also, that the results of the REACH trial, an international trial comparing the same drug combinations as second or subsequent line treatment will also be announced, although this did not reach its primary endpoint at its first interim analysis, it is believed that it did so shortly afterwards at its final analysis.

I predict (with no inside information) that both will show that FCR gives a higher rate of complete remissions and longer first remissions than FC, though as yet there will be no difference in overall survival.

Which all makes the paper from Houston on the long term follow-up of patients treated with FCR all the more significant. It is published this week in Blood 2008; 112:975-980.

The headline results show a 95% response rate with 72% complete remissions. Even better they claim that the bone marrow was free of minimal residual disease in 82% by flow and 42% by PCR. These good responses are backed up long remissions. The actuarial overall survival at 6 years was 77% and the actuarial failure-free survival at 6 years was 51%. Among patients who achieved a partial response or better the median time to progression was 80 months with a projected progression free survival at 6 years of 60%.

These figures are so good that before we start jumping for joy, we need to ask whether there was anything unusual about the patients treated. Between 1999 and 2003 they treated 300 previously untreated patients. These were patients with symptomatic or progressive disease as defined by the 1996 NCI guidelines. 36% were Rai stage III or IV (Binet stage C), 61% were Rai stage I or II and 4% stage 0. Rai staging does not give quite the same measure of tumour bulk as Binet staging, so it is impossible to say how many of those stage I or II patients would have been Binet A or B. A patient who is stage 0 could have retroperitoneal glands, or symptoms or a rapid lymphocyte doubling time.

NCI guidelines are open to a degree of interpretation when such factors as fatigue, night sweats and lymphocyte doubling time are considered. It should also be remembered that the American patient population is very well informed of every new development and often has an eagerness to try anything new. Houston has a reputation for being go-ahead and innovative and certainly attracts such patients.

The median age of this group was 57 years and only 14% of patients were over 70. Although far more patients with CLL are over-70 (perhaps as many as two-thirds) many of these older patients die on other conditions while still on the watch and wait programme, so one would expect treated patients to be younger than the CLL population as a whole. In order to make an assessment of this, I looked at our own series in Bournemouth. For us the median age at first treatment was 64 (range 21-97) and 36% of those treated were aged 70 or over. We can conclude therefore that the Houston patients were rather younger than the patients that most people treat.

This was a group who were selected before most prognostic markers became available so there will be no data on *IGHV* genes, ZAP-70 or FISH. Conventional karyotyping was performed on 222/300 but since only 30% had clonal abnormalities, we can be sure therefore that the karyotyping was suboptimal. Nevertheless, 4% had abnormalities involving chromosome 17. Only 21% had a CD38 >30% and only 43% had a β_2-microglobulin at more than twice the upper limit of normal.

I hope that in the near future we will be able to get access to the LRF CLL4 trial to compare the number of patients who had high Beta-2M levels, but I do not have that information on our own series.

Again I was able to compare this group with our own, in terms of CD38. In our series 64% had a CD38 >30%. From this is seems likely that the Houston group of patients had a less severe type of CLL than most people would find themselves treating. In the Houston series factors associated with a longer survival were age less than 70; Beta-2M levels less than twice normal; white counts less than 150; and the absence of chromosome 17 abnormalities.

How about the very impressive figures for absence of minimal residual disease? The flow method just looked at CD19/CD5 positive cells, which is very insensitive, picking up only 1 in 100; this compares with four colour flow, which has a sensitivity of 1 in 10,000 or even 1 in 50,000. Even the PCR method used here seems a bit insensitive, claiming a detection of 1 in 10,000 where others expect 1 in 100,000.

These results, therefore, come with a bit of a health warning. Others may not expect to obtain such encouraging results with FCR.

The good news is that they have looked carefully at other possible complications of FCR such as MDS and Richter's syndrome. The actuarial risk of Richter's syndrome was 2.5% at 6 years, little different to what has been seen historically. The risk of MDS was about the same. The major complication of FCR was prolonged cytopenia. Following completion of therapy 19% of patients had persistent cytopenia (neutrophils less than 1 or platelets less than 50) lasting more than 3 months. After recovery of counts recurrent late cytopenic episodes occurred in 28%, predominantly in the first year. These episodes did not presage the development of MDS in most cases. The risk of serious or opportunistic infection was 10% and 4% during the first and second years of remission respectively.

This paper is very helpful in letting us know what will happen when we start treating patients in the UK in large numbers with FCR. I anticipate that this might occur in late 2009 or early 2010.