Controversy I: controversies in follicular lymphomas

a) A TREATMENT IS NECESSARY IN FL: SHOULD WE START WITH R-CT OR IS RITUXIMAB ALONE SUFFICIENT?

004 IF TREATMENT IS NECESSARY IN FL: SHOULD WE START WITH R-CT OR IS RITUXIMAB ALONE SUFFICIENT?

R. I. Fisher
James P. Wilmot Cancer Center, Rochester, NY, United States

The last decade has resulted in significant improvement in the prognosis of patients with advanced stage follicular lymphoma. The old paradigm, that the median survival for these patients ranged from 5-7 years with no plateau in the survival curve, no longer remains valid. Fisher et al. demonstrated that sequential studies conducted by SWOG demonstrated improved survival over the past several decades. At the current time five-year survival exceeds 80% for these patients. Similar results have been obtained by the German Low-grade Non-Hodgkin's Lymphoma Group and the M.D. Anderson hospital. The introduction of chemoimmunotherapy containing Rituximab has significantly improved the overall prognosis of these patients. Marcus et al. demonstrated improved time to treatment failure and borderline improvement in overall survival when patient's received R-CVP. Similar results were obtained by the German Low-grade Lymphoma Group utilizing R-CHOP. A meta-analysis of R-chemotherapy has demonstrated consistent improvement of pfs with R-chemoimmunotherapy with an early trend toward improved overall survival. Maintenance Rituximab for up to 2 years following the completion of R-chemotherapy has also demonstrated improved pfs and a non-significant improvement in overall survival. Furthermore if one analyzes the prima data, it becomes clear that patients were treated with R-CHOP do better than patients treated with R-CVP. Therefore if individual studies and population studies both show improvement in overall survival is it still reasonable to state that the initial treatment choice does not matter? Is it still reasonable to only attempt to achieve partial remissions with disease control for a period of time? Should a minimal residual disease status be the target of our initial treatment? Would Rituximab alone or Rituximab plus chemotherapy be most likely to produce long-term failure free survival? What is the difference in the incidence and timing of transformation with patients treated with Rituximab alone or Rituximab combined with combination chemotherapy? Direct comparative data are clearly not yet available; however physicians should carefully consider the age, performance status, extent of disease etc. For patients with follicular lymphoma beginning initial treatment in 2011.

005 SINGLE AGENT RITUXIMAB IS A VALID OPTION FOR FIRST-LINE TREATMENT IN FOLLICULAR LYMPHOMA

M. Ghielmini
Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

If we accept that follicular lymphoma remains an incurable disease, (with the exception of the few cases which are possibly cured with bone marrow transplantation) then the purpose of treatment is prolongation of survival and optimisation of the quality of life.

Treatments which have shown to prolong survival are those involving the immune system: Interferon alpha, rituximab and allogeneic transplantation.

If Interferon could show its survival-increasing capacity only when associated to first-line chemotherapy, both rituximab and allo-transplant can obtain this life-prolonging effect also when used in second or further lines. For rituximab this is true both when given together with chemotherapy and when given as a maintenance. It follows that what is important for an FL patient is that he receives rituximab, independently of chemotherapy. We can even say that it was demonstrated that one needs rituximab on top of chemotherapy but we are still not sure that we need chemotherapy on top of rituximab.

Nowadays the median overall survival of follicular lymphoma has risen from 10 to approximately 15 years. It becomes therefore more and more true that FL patients live a long time and are exposed, as Hodgkin's lymphoma patients, to the potential long-term side effects of chemotherapy. Delaying chemotherapy is therefore a way of ameliorating quality of life both by postponing the acute and the long-term side effects of cytotoxic treatment.

A recent study by the BNLI could very well show that single-agent rituximab can postpone the initiation of chemotherapy by several years.

In conclusion we believe that patients with follicular lymphoma will sooner or later need chemotherapy, but that many of them, if not in need of a very rapid response, a course of single agent rituximab followed by rituximab maintenance gives a chance of conserving a good quality of life while delaying the side-effects of chemotherapy, all without losing any survival advantage.

b) MAINTENANCE IN FL: RIT OR RITUXIMAB?

006 RADIO-IMMUNOTHERAPY CONSOLIDATION VERSUS RITUXIMAB-MAINTENANCE IN FIRST REMISSION FOLLICULAR NON-HODGKIN'S LYMPHOMA. THE CASE FOR RIT.

A. Hagenbeek
Hematology, Academic Medical Center, Amsterdam, Netherlands

This forthcoming debate deals with the battle between ''cold'' and ''hot'' antibodies in first remission follicular NHL or – to be more precise -Rituximab-maintenance for a prolonged period of time versus a single infusion of a radio-labelled anti-CD20 monoclonal antibody. Only a few large randomized trials with newly diagnosed patients with follicular NHL have been reported recently. From my perspective, the core of the debate focuses on the comparative evaluation of the ECOG 1496 study and the FIT trial. In the ECOG study newly diagnosed patients with indolent (mainly follicular) lymphoma were induced with CVP and responders were subsequently randomized between R-maintenance, once per week for 4 weeks every 6 months x4 (1); in the FIT trial various chemo-induction regimens were allowed after which PR and CR patients were randomized between one infusion of Zevalin versus no further treatment (2). Obviously, there was pronounced hematological toxicity in the FIT trial, which was – however – manageable. No patients died from toxicity. CR rates after induction were 16% (ECOG) versus 52% (FIT), increasing to 37% (ECOG) and 87% (FIT), due to 22% and 78%, respectively, of patients in PR converting to CR. With more than 4 yrs (ECOG) and 6.5 yrs (FIT; 3) median follow-up, the median PFS was prolonged by 3 years in both studies as compared to controls. In patients achieving a CR after Zevalin, the PFS increased more than 5 years as compared to controls (median PFS > 92 months after 1 infusion of Zevalin. . ..). This has never been shown before with any other single agent. Thus, a single infusion of Zevalin matched roughly 4 x 4 = 16 infusions of Rituximab in terms of achieving the same increase in PFS. I leave it up to the audience to draw conclusions about cost-effectiveness . . .

As the FIT trial was initiated in 2001, only a relatively small fraction of the patients (14%) was induced with R-chemo. Thus, the question arises whether Zevalin is effective after R-chemo induction as this is standard treatment to date. To this end, it was observed that 71% of the R-chemo patients converted from PR to CR after Zevalin and showed a longer PFS as compared to controls. Similar conversion rates were reported from phase II studies in which Zevalin consolidation was given after R-chemo induction. These observations, and others to be presented, make it quite likely that Zevalin works after R-chemo as long as there are accessible CD20- positive targets.

Thus, in conclusion, RIT represents the most effective single ''drug'' in the treatment of follicular NHL. No doubt about it.

Finally, in this context results of the less mature PRIMA trial will be discussed and a proposal will be put forward on how ''cold'' and ''hot'' might fight side-to-side in defeating follicular NHL.

1. Hochster et al., JCO 27 (2009) 1607-1614
2. Morschhauser et al., JCO 26 (2008) 5156-5164
3. Hagenbeek et al., ASH abstract 594, 2010
4. Salles et al., the Lancet 377 (2011) 42-51

007 BACKGROUND FOR THE POSITIVE POSITION FOR RITUXIMAB MAINTENANCE

E. Kimby
Center of Hematology, Karolinska University Hospital, Stockholm, Sweden

Rituximab has become part of first-line treatment in most patients with follicular lymphoma as several prospective trials have shown benefits both in progression-free survival (PFS) as well as in overall survival compared to chemotherapy alone. Also the use of rituximab as maintenance has shown benefits in several trials with a consistent marked prolongation of PFS with minimal toxicity. This benefit has occurred whether maintenance follows single-agent rituximab or combination chemotherapy. A randomized clinical trial comparing induction therapy with single-agent rituximab 375 mg/m(2) once per week x 4, versus the same induction followed by one infusion of maintenance every 2 months x4, showed that 45% of the patients responding to the induction were still event-free at 8 years with prolonged exposure to rituximab (Martinelli et al JCO 2010).

Patients with relapsed/resistant FL responding to CHOP or R-CHOP induction have a superior PFS with rituximab maintenance, confirmed also after a median follow-up of 6 years (van Oers et al JCO 2010).

According to the results of the large intergroup ''Primary Rituximab and Maintenance'' [PRIMA] trial, maintenance with rituximab during 2 years improves PFS significantly in pts with previously untreated FL responding to

immunochemotherapy (Salles et al Lancet 2011). Almost 80% of the patients had intermediate-risk or high-risk FLIPI scores and all had indications for therapy. In total, 1019 patients achieved a complete or partial response to R-CHOP (n=768), R-CVP (n=222) or RFCM (n=28) and were randomly assigned to receive 2 years of rituximab maintenance therapy (375 mg/m(2) every 8 weeks) or observation. After a median follow-up of 36 months, PFS was 75 % in the rituximab maintenance group (130 patients progressed) and 58 % in the observation group (218 progressed), a highly statistical difference. Time to next antilymphoma treatment was also longer in the maintenance group than in the observation group.

With rituximab maintenance a slightly increased rate of infections, mostly non-severe, has been reported and with prolonged maintenance concentrations of IgM has been shown to fall, and also IgG deficiencies has been described in a few patients. Otherwise the maintenance has been well tolerated.

In summary there is evidence for supporting the use of rituximab maintenance.