Rituximab For The First-Line Treatment Of Stage III-IV Follicular Lymphoma (Review Of TA 110)

Personal Statement

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Introduction

I was appointed a Consultant Haematologist at Glasgow Royal Infirmary in 1999, having previously worked as a trainee haematologist in a number of different centres including Glasgow, Nottingham, Leicester and Northampton. I am lead clinician for haemato-oncology in Greater Glasgow & Clyde Health Board. I personally manage patients with lymphoma from the east end of Glasgow (population approx 200,000) and participate in the north Glasgow multidisciplinary meetings discussing all lymphomas (catchment approx 600,000) as well as the West of Scotland lymphoma MDT for complex cases, which covers a population of approx 2.5 million. I am also a member of the Glasgow Adult Transplant team and as part of this workload give high dose therapy with stem cell rescue (autologous transplant) for the West of Scotland and allogeneic transplants for Scotland to patients with relapsed/ refractory follicular lymphoma.

The following is a personal statement detailing my perception of the impact of the use of Rituximab in first line treatment of stage 3/ 4 follicular NHL rather than a literature review.

Follicular NHL

Grade 3 / 4 Follicular NHL is said to be an incurable disease unless an allogeneic transplant is used, however the latter carries a significant morbidity and mortality and is virtually never indicated as part of first line therapy(Thomson, Morris et al. 2010). The prognosis for follicular NHL is extremely variable with a median survival of at least 10 years, but there will be some who have a much poorer outcome, and many patients will require multiple lines of therapy during those years. The advent of the Follicular Lymphoma International Prognostic Index has helped somewhat in determining who will do poorly (36% 10 year overall survival), but is less useful in identifying patients who will do very well (76% 10 year overall survival)(Solal-Celigny, Roy et al. 2004). We are still learning why there is such a huge variation in outcome and time to disease progression, but it is probably dependent on the biology of the lymphoma (Dave, Wright et al. 2004; Taskinen, Valo et al. 2010). In addition for all patients there is the risk of transforming to a higher grade diffuse large B cell lymphoma, which carries a considerably poorer prognosis(Montoto, Davies et al. 2007). However, we do know that the duration of disease free survival is partially dependent on the amount of residual disease burden at the end of therapy(Bachy, Brice et al. 2010). It has been shown that even refractory/ relapsed patients post high dose therapy, who have achieved maximal response radiologically and with no disease detectable by molecular techniques (MRD), have prolonged periods in remission often lasting many years (Ladetto, Vallet et al. 2006; Arcaini, Montanari et al. 2008). However, such intensive treatment has a mortality of about 2-5% in the short term and a significant potential for major long term sequelae and therefore if used as first line therapy it does not improve overall survival (Deconinck, Foussard et

al. 2005; Ladetto, De Marco et al. 2008). It is therefore reserved for younger, fitter patients who have demonstrated aggressive disease with early progression and who are able to withstand such therapy in which the risks can be justified and is not used first line unless there is a poor response to initial therapy. Therefore the aim of therapy should be to improve CR rate as well as increasing MRD responses, but without increasing toxicity, thereby improving overall survival.

My experience is that patients usually have the best quality of life following their first line therapy, if they have had a good response. Each subsequent regimen causes a reduction in fitness, increases possible toxicity such as poor bone marrow recovery, recurrent infections and also more problems returning to work, regaining psychological balance etc.. We should therefore be looking to prolong the time in first response.

Rituximab

The introduction of Rituximab to the management of B cell derived lymphomas has substantially altered clinical outcomes since I became a consultant. I have seen personally the impact of the addition of Rituximab to CVP in stage III & IV follicular NHL on duration of remission and quality of life with more recently maintenance following first and second line therapy. This improvement has been well documented in many different clinical trials. The addition of R to CVP shows an improvement in quality of life (Marcus, Aultman et al. 2010) as well as in progression free survival(Marcus, Imrie et al. 2005) with improved achievement of CR. This has been further improved with the addition of maintenance rituximab(Salles, Seymour et al. 2011).

Rituximab is surprisingly non-toxic in terms of increasing infection risk when combined with chemotherapy both during and after therapy. The antibody infusion is well tolerated by the majority of patients with only a small minority developing intractable allergic reactions to Rituximab necessitating abandoning it's use in further treatment. The addition to any chemotherapy regimens does not appear to increase toxicity significantly.

Chemotherapy Regimens

There are data to support a number of different chemotherapy regimens for the treatment of follicular NHL, both at diagnosis and relapse, but CVP has been the standard regimen for many years in the UK. However, there is increasing use of CHOP and in the recent PRIMA study R-CHOP was the commonest regimen and the one which had the best improvement in PFS when maintenance Rituximab was given(Salles, Seymour et al. 2011). In addition the use of CHOP combined with Rituximab shows improved overall survival when compared with CHOP alone(Hiddemann, Kneba et al. 2005) and whilst never compared head to head ORR and PFS appear to better with R-CHOP compared to R-CVP. It is already my practice in patients with higher grade histology 3b to use R-CHOP as there appears to be a reduction in transformation to diffuse large B cell NHL as well as improvement in PFS. The regimen is a little more toxic in terms of neutropenic sepsis, but is well tolerated.

However, not all patients can be given full dose cyclophosphamide or doxorubicin because of liver dysfunction either due to disease or associated co-morbidities. In these instances either dose reduction or agents such as fludarabine can be used(Montoto, Moreno et al. 2008) with good disease control. There are also individuals not fit enough for CVP or too old to deal with the toxicities of CVP for whom single agents such as bendamustine, cyclophosphamide or chlorambucil are appropriate, but who would benefit from the addition of Rituximab to this regimen.

Conclusions

I feel that the restriction of the current NICE and SMC guidance to RCVP as the sole approved regimen for stage 3/ 4 patients as first line is a poor use of resources and detrimental to outcome for some patients. R-CHOP and R-FCM both show excellent efficacy in the treatment of follicular lymphoma and may have better progression free survival than R-CVP, but the resources required to carry out a randomised phase 3 trial mean that this is unlikely to ever be carried out(Montoto, Moreno et al. 2008). There is data supporting the use of Rituximab in combination with many different chemotherapy regimens and in all cases there is a significant benefit for progression free survival and, with time, I suspect that an improvement in overall survival will also become apparent.

I think that to maximise the benefit of the Rituximab given as first line therapy we should be looking to use Rituximab in combination with CHOP or other similar regimens in patients who are fit and under 70-75 thereby increasing the duration of that crucial first response phase where quality of life is best (Hiddemann, Kneba et al. 2005). For those who are less fit or over 70-75 we are currently using rituximab inefficiently, which is not cost effective. Rituximab can be given as single agent first line therapy, but would be more effective if given in combination with chlorambucil or bendamustine (Rummel, Al-Batran et al. 2005).

By removing the restriction on chemotherapy regimen it should be easier possible to maximise the initial depth of response for every patient whatever age with minimal increase in toxicity and therefore increase the numbers achieving MRD and prolonging that crucial first period in remission possibly indefinitely for some patients.

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