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Update of alemtuzumab in the treatment of chronic lymphocytic leukaemia

Introduction

Chronic lymphocytic leukaemia (CLL) is the commonest of the adult leukaemias in the western world. The clinical course is highly variable with some patients surviving decades without requiring therapy whilst others have more aggressive disease requiring immediate treatment and associated with a shortened survival. Conventional treatment has relied on alkylating agents such as chlorambucil and, more recently, purine analogues such as a fludarabine. As single agents these therapies achieve good overall response rates (OR) of up to 80% but with complete remission rates (CR) of <10% for chlorambucil and 15-20% for single agent fludarabine. Combinations of these drugs, such as fludarabine together with cyclophosphomide, have shown increase in complete remission rates up to 40% with a prolongation of progression-free survival (PFS).[1] However, none of the randomised studies have shown any survival advantage. This latter observation is largely due to the ability to successfully re-treat relapsed patients. However, patients who become refractory to alkylator and fludarabine based treatments have traditionally had a very poor response (<20%) to salvage therapy and a greatly shortened survival (median 10 months).[2]

Over the past decade outcome for this group of chemo-refractory patients has been improved by the introduction of novel agents including monoclonal antibodies. Alemtuzumab is a fully humanised monoclonal antibody directed against the CD52 antigen which is widely expressed on B- and T-lymphocytes. It is licensed for the treatment of fludarabine refractory CLL and has been shown to induce remissions in 33-53% of patients in this setting.[3,4] The standard dosing schedule is of 30 mg given three times a week intravenously for 12 weeks.

Alemtuzumab monotherapy

A number of Phase II trials using alemtuzumab in relapsed/refractory CLL have been published.[3-6] There are no Phase III trials in this group. The pivotal study enrolled 93 patients and showed an overall response rate (ORR) of 33% (2% complete remission). Median overall survival (OS) was 16 months and 32 months for responders.[3] This led to the license of alemtuzumab for relapsed/refractory CLL. A German study enrolling patients with similar characteristics used the sub-cutaneous route of administration and showed the same

efficacy (ORR of 35%) with reduced infusional toxicity.[6]

The first report of the use of alemtuzumab as frontline therapy was in 1996 by Osterborg *et al*.[7] Nine patients received the standard treatment, although in 4 patients the antibody was administered subcutaneously, and therapy was continued in all patients up to 18 weeks. The overall response (OR) rate was 89% with 3 patients achieving a complete remission (CR). This group expanded the patient cohort and reported a further 41 patients treated with subcutaneous alemtuzumab as first line therapy for a total of 18 weeks.[8] The OR rate was maintained at 81% in 38 evaluable patients. 19% of patients achieved CR and 68% a partial remission (PR). At the time of publication in 2002 the time to treatment failure had not been reached at 18+ months. These results are comparable to those observed for single-agent fludarabine[9] and superior to those for single-agent rituximab[10] (Table 1). Interestingly, complete responders required 18 weeks of therapy to achieve their best response, with significant improvement in bone marrow clearance between the 12 and 18 week evaluation points. Furthermore, patients with low volume lymphadenopathy also achieved complete remissions in contrast to the observation in relapsed refractory patients that lymphadenopathy predicted for poor response to single-agent antibody treatment. 10% of patients developed CMV reactivation which responded rapidly to treatment with intravenous ganciclovir. There was no increase in bacterial sepsis. Although transient injection site reactions were observed with the subcutaneous administration in the majority of patients many of the initial reactions associated with intravenous administration such as rigors, nausea and hypertension were not seen. 1 in 5 patients had a transient grade 4 neutropenia but other side effects were rare.

Table 1. Response rates for single agent front-line therapy in CLL.

Agent	*OR*	*CR*	*Ref*
Chlorambucil	55%	2%	11*
Alemtuzumab (IV)	83%	24%	
Alemtuzumab (SC)	87%	19%	8
Fludarabine	63%	20%	9
Rituximab	51%	4%	10

**CAM307 phase III prospective randomized trial comparing chlorambucil and alemtuzumab*

An international prospective randomised controlled trial (CAM307) comparing chlorambucil with intravenous alemtuzumab as front line therapy for CLL were reported last year.[11] 297 patients were randomised to receive either alemtuzumab at the standard dose of 30 mgs 3x per week for up to 12 weeks or chlorambucil 40 mgs/m^2 once every 28 days up to 12 cycles. Response rates assessed by an independent panel showed OR of 83% for alemtuzumab compared to 50% for chlorambucil with CR rates of 24% and 2% respectively. (Table 1) This translated into improved PFS for the patients who received alemtuzumab with a 43% lower risk of progression or death. Notably, for patients who had the cytogenetic deletion of 17p (p53), there was a threefold increase in OR with alemtuzumab (64%) compared with chlorambucil (26%). Statistically significant superior responses were also seen for patients with deletion 13q and deletion 11q treated with alemtuzumab compared with chlorambucil. Infections, including CMV, were reported in 76% of patients receiving alemtuzumab compared with 50% of chlorambucil patients whilst on study. Grade 3 and 4 lymphopenia and neutropenia were more common with alemtuzumab but anaemia and thrombocytopenia were similar in the two treatment groups. Episodes of bacterial sepsis and febrile neutropenia were comparable and the increase in infection in the alemtuzumab arm was almost entirely attributable to CMV reactivation. Although CMV reactivation occurred in half the patients this was only

symptomatic in 16%. This toxicity was therefore manageable by screening and pre-emptive treatment. Grade 3 or 4 infusional related events were seen in 13% of patients receiving alemtuzumab and these were largely confined to the first few weeks of therapy. In contrast, adverse events increased over time in the chlorambucil arm where the median duration of treatment was twice as long. The toxicity profile of alemtuzumab in previously untreated patients appears to be much more acceptable with no increased treatment related mortality compared with chlorambucil in the CAM307 randomised study. Based on this trial the FDA and EMA have licensed alemtuzumab for first line treatment of CLL. The Lundin study showed that efficacy for 18 weeks of subcutaneous alemtuzumab was equivalent to 12 weeks of intravenous therapy on CAM307. Since subcutaneous administration results in fewer infusion related side effects, this may be the preferable route.

Alemtuzumab consolidation therapy

Studies of alemtuzumab treatment of CLL, particularly in the relapsed/refractory setting, have consistently shown that patients with bulky nodal disease are less likely to respond to treatment compared with those patients who have low volume or no lymph node enlargement. This is in contrast to the excellent clearance of disease from the blood and bone marrow. In addition, in the Moreton study,[5] patients who achieved complete remissions and who were also negative for minimal residual disease (MRD) using a sensitive four-colour flow cytometry[12] had significantly prolonged PFS and overall survival (OS). Several studies have confirmed the observation that those patients achieving MRD-negativity have prolonged remissions compared with those patients who are MRD-positive at the end of therapy.[13-15] This has provided a rationale for using alemtuzumab as consolidation of remissions achieved using fludarabine- based induction regimens. Four groups have published their results for this strategy using various treatment schedules, doses and routes of administration[16-19] (Table 2). Although not comparable all have demonstrated the efficacy of such an approach in improving responses in around 50% of patients receiving consolidation. In addition , alemtuzumab has been used as an *in vivo* purge to reduce the numbers of contaminating CLL cells in patients post-induction therapy who then proceeded to successful PBSC collection , in some cases followed by high dose therapy and autologous stem cell rescue

Table 2. Alemtuzumab consolidation therapy.

Study	*Median interval from chemo-therapy to maintenance*	*Route*	*Dose*	*Improved response*
Wendtner (2004)[16]	67 days (45-90)	IV	30 mg TIW	45%; improved PFS
O'Brien (2003)[17]	6 months (1-40)	IV IV	10 mg TIW 30 mg TIW	39% 56%
Rai (2002)[18]	~2 months	IV/SC	30 mg TIW	92% OR; 42% CR/44%
Montillo (2004)[19]	At least 8 weeks after F	SC	10 mg TIW	51%

TIW= three times a week; OR= overall response; CR = complete response, F= fludarabine, IV= intravenous; SC= subcutaneous.

There has only been one randomised study of alemtuzumab consolidation which was reported by the German study group in 2004[16] and updated at ASH in 2006.[20] Patients who had been treated to maximum response with fludarabine or fludarabine plus cyclophosphomide were randomised to receive alemtuzumab at the standard dose of 30 mg 3 x per week for 12 weeks given intravenously at a median of 2 months following induction treatment or to have no further treatment. The trial was stopped prematurely having recruited 21

patients (11 to alemtuzumab and 10 to observation) because of a high infection rate in the alemtuzumab arm. However, despite the small numbers of patients, this trial did show a significant improvement in PFS for patients receiving alemtuzumab consolidation (median not reached) compared with 27.7 months for the observation arm. At the ASH meeting in 2007 the CALGB group reported significant toxicity for the same consolidation regimen given within 3 months of completing induction treatment with fludarabine and rituximab.[21] Factors contributing to the toxicity of alemtuzumab in this setting may be the dose and duration of therapy and, most importantly, the short interval between completing induction treatment and introduction of consolidation. This needs to be taken into consideration when planning future studies.

Consolidation after first induction treatment of CLL is therefore feasible and can deepen remission and increase PFS in a proportion of patients. However there is a risk of toxicity and there are also financial implications. It may therefore be prudent to reserve this strategy for those patients with higher risk disease. Furthermore, a larger randomised study needs to be completed in such a group to confirm safety and efficacy as well as establishing the optimal timing, dose and delivery (IV or SC).

Alemtuzumab for high risk CLL

It is well recognised that patients who have deletions of chromosome 17p resulting in dysfunction of the p53 pathway have resistance to conventional chemotherapy such as alkylating agents or purine analogues and also have significantly shortened survival compared with those patients without this abnormality.[22] Although p53 deletion in CLL is infrequent at initial presentation, occurring in 5-10% of patients, this abnormality becomes increasingly common as the CLL advances and becomes chemo-resistant. There have now been a number of reports showing that alemtuzumab has efficacy in this subgroup, probably by killing cells through a p53-independent mechanism, with responses seen in about half of patients.[23-25] The only other therapy shown to be effective in this way is high-dose steroid.[26] In CLL patients with p53 deletion who do not have bulky nodal disease single-agent alemtuzumab may be an appropriate treatment choice either at first or subsequent line of therapy. However, in those patients with enlarged nodes it would seem logical to combine alemtuzumab with high-dose steroids and this regimen does appear to be effective in a small number of patients who have been treated.[27] It is important therefore that patients who are about to embark on treatment, whether this is first or subsequent line, should have analysis to detect the presence of the p53 deletion. The knowledge of specific genetic abnormalities will allow the prospective selection of appropriate treatments in order to reduce the damage caused by ineffective chemotherapy and to maximise the opportunity for achieving a good remission.

Alemtuzumab combination regimens

Combination of antibodies with conventional chemotherapy regimens has resulted in an exciting advance in the treatment of haematological malignancies. In CLL vey high ORR, CR and PFS have been reported for the combination of rituximab (anti-CD20 antibody) with the FC regimen given first line.[28] To date experience with alemtuzumab in combination regimens is somewhat limited and has mainly been explored in the relapsed patient setting. Data of combinations with fludarabine (FluCam- fludarabine and alemtuzumab;[29] FCC- fludarabine, cyclophosphamide and alemtuzumab;[29]

C-FAR- cyclophosphamide, fludarabine, alemtuzumab and rituximab[31] and with rituximab[32] have all shown improved efficacy when compared with alemtuzumab as a single agent in an equivalent clinical setting. There are currently a number of trials, including Phase III studies, examining fludarabine/alemtuzumab based combinations in the first and subsequent line setting and the results of these are awaited. Studies of high-dose steroids and alemtuzumab in high risk (p53 del) CLL are on-going.

Conclusions

There have been major advances in the management of CLL over the past decade. This includes both the ability to stratify patients according to biological risk parameters, such as genetic abnormalities, the introduction of novel therapies such as monoclonal antibodies and the ability to achieve a high proportion of very good remissions including eradication of minimal residual disease. All these strategies have resulted in improved selection of patients for appropriate therapy and better PFS. Alemtuzumab has been shown to be an effective monotherapy in both first line and refractory CLL and it is now clear from several studies that toxicity is much reduced and more manageable when alemtuzumab is used earlier in therapy. More data is now needed on the use of alemtuzumab in front-line combination regimens. The most compelling data for alemtuzumab efficacy is in the high risk cytogenetic group exhibiting p53 deletion when used either as a single agent or in combination with high-dose steroids. In addition this antibody therapy has been shown to be very effective in eradicating residual disease after completion of induction therapy, although the optimal regimen (dose, schedule and route of administration) is still to be determined.

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