Ofatumumab in advanced stage chronic lymphocytic leukaemia: results of the UK named patient compassionate use programme

We report our ‘real life’ experience of the use of Ofatumumab in chronic lymphocytic leukaemia (CLL) in the UK compassionate use programme. In addition to patients with bulky fludarabine refractory (BF ref) disease ($n = 12$) or fludarabine and alemtuzumab refractory (FA ref) disease ($n = 4$), patients unsuitable for alemtuzumab were included ($n = 6$). 91% of transfusion dependent patients became transfusion independent. The overall response rate (ORR) was 48% (3/27 clinical CR; 10/27 PR). 4/6 patients with TP53 deletion/mutations responded to Ofatumumab. This is the first series of UK patients confirming that single agent Ofatumumab has efficacy in relapsed refractory CLL and will complement on-going clinical studies.

Although thought to be an indolent disease of the elderly, a significant number of patients with chronic lymphocytic leukaemia (CLL) develop chemotherapy resistance and die from bone marrow failure and infectious complications. Ofatumumab (HuMax-CD20) is a fully humanized anti-CD20 monoclonal antibody with promising activity in B-cell disorders including CLL. It binds to a different epitope to Rituximab and is thought to confer greater complement-mediated cellular cytotoxicity with some additional antibody-dependent cellular cytotoxicity (Cheson, 2010). A recent interim analysis of the first 138 patients entered into the single arm Phase II study Hx CD20 406, evaluated its safety and efficacy in BF ref or FA ref disease (Wierda et al., 2010). Patients unsuitable for alemtuzumab were excluded. The overall response rate (ORR) was 58% in the FA ref group and 47% in the BF ref group. Perhaps the most significant improvement was in overall survival, which was 13 and 47% in the BF ref group. Perhaps the most significant overall response rate (ORR) was 58% in the FA ref group.

Treatment was well tolerated with very few significant side effects recorded. Two patients developed a further malignancy (one basal cell carcinoma and one malignant melanoma). The three early patient deaths were secondary to severe lower respiratory tract infections and underlying immunosuppression. The median time to reach a haemoglobin level $>110$ g/l was 21 days. Twelve patients had a platelet count $<100 \times 10^9$/l prior to treatment. Following Ofatumumab, nine patients had a platelet count $>100 \times 10^9$/l (Table I). The median follow up was 80 months (range 1–23 months) from the onset of the Ofatumumab infusions. Three patients achieved a clinical complete remission (CR) and 10 patients a partial remission (PR). Nine patients had progressive disease, two stable disease and three died. The overall response rate was therefore 48% (13/27). The median time-to-next-treatment (TTNT) when calculated from the first Ofatumumab infusion was 5.5 months (range 1.5–18) (Table I and Fig 1).

Interestingly, 4/6 patients with TP53 mutations/deletions responded to single agent Ofatumumab. Two of them had the longest TTNT of all patients treated.

Chronic Lymphocytic Leukemia guidelines (Hallek et al, 2008). Improvement of peripheral blood cytopenias and reduction in red cell and platelet transfusion requirements were recorded.

A total of 27 patients with a median age of 65 (range 48–83) years were treated. The median disease duration was 6 years (range 3–15), with a median number of three previous treatments (range 0–6). 22.2% of patients were Rai stage I–II, the remainder stage III–IV. There were no Binet stage A patients, with 25% being Binet stage B and 75% Binet stage C. Cytogenetic data was available on 24 patients. Six patients had no discernible abnormality, two patients had trisomy 12, two patients del13q14.3, seven patients del11q22.3 and six patients del17p13.1. Twelve patients had bulky refractory disease, four had double refractory disease, five had both bulky refractory and double refractory disease and six were considered unsuitable for Alemtuzumab therapy.

Three patients died after receiving one or two infusions. These were classified as non-responders. 11/12 patients, who were red cell dependent prior to Ofatumumab therapy, became transfusion independent. The median time to reach a haemoglobin level $>110$ g/l was 21 days. Twelve patients had a platelet count $<100 \times 10^9$/l prior to treatment. Following Ofatumumab, nine patients had a platelet count $>100 \times 10^9$/l (Table I). The median follow up was 80 months (range 1–23 months) from the onset of the Ofatumumab infusions. Three patients achieved a clinical complete remission (CR) and 10 patients a partial remission (PR). Nine patients had progressive disease, two stable disease and three died. The overall response rate was therefore 48% (13/27). The median time-to-next-treatment (TTNT) when calculated from the first Ofatumumab infusion was 5.5 months (range 1.5–18) (Table I and Fig 1).

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Treatment was well tolerated with very few significant sides effects recorded. Two patients developed a further malignancy (one basal cell carcinoma and one malignant melanoma). The three early patient deaths were secondary to severe lower respiratory tract infections and underlying immunosuppression. Three patients developed reversible peripheral neuropathies.

As far as we are aware, this is the first report of the use of Ofatumumab in a compassionate use programme. Overall, the results presented are comparable with those from the interim analysis of the Phase II study (Wierda et al., 2010).
responders, Ofatumumab showed rapid response rates. The median response duration was short. However two patients had a prolonged response of 18 months; both carried TP53 mutations/deletion. There is additional in vitro data supporting the hypothesis that Ofatumumab has activity against CLL cells with TP53 mutations/deletions (Zenz et al., 2010). Larger studies in TP53 deleted/mutated patients are required to fully evaluate the role of Ofatumumab in this patient group.

Ofatumumab therapy resulted in few side effects, although three of our patients developed reversible peripheral neuropathies. This is a previously unrecognized side-effect that is of interest, as Rituximab is used in the treatment of demyelinating polyneuropathies (Tracy & Dyck, 2010).

In conclusion, we believe that our observations extend the results of the Phase II interim analysis of Hx CD20 406 and illustrate that Ofatumumab shows efficacy in refractory CLL and is well tolerated. However, response duration is short and studies to evaluate its role in combination therapy for previously untreated CLL and Richter transformation are on-going. Maintenance therapy with Ofatumumab might become one approach to improve response durations to this promising novel antibody.

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**Authorship Contributions**

OC and AS analysed the data and wrote the manuscript. AV, JP, PC, AB, GAF, PH and AS, all recruited patients and

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**Table I. Treatment results.**

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Median TTNT from last Ofatumumab infusion (months)
- Range 1–5–18
- ≤3 months 6
- 4–11 months 8
- ≥2 months 3
- Not reached 9
- Elective allograft 1
- Overall Response Rate (CR and PR) 13 (27)

CR, complete remission; PR, partial remission; PD, progressive disease; SD, stable disease; LRTI, lower respiratory tract infection; TTNT, time to next treatment.

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collected data. All authors reviewed and accepted the manuscript.

Disclosure of Conflicts of Interest

PH has received honoraria from GSK and Roche. AB has received honoraria from GSK. AS has received honoraria from GSK, ROCHE and Genzyme.

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References


