Five-year survival follow-up of a phase III randomised trial comparing ofatumumab versus physicians’ choice for bulky fludarabine-refractory chronic lymphocytic leukaemia: a short report

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Summary

In 2014, an interim analysis of a phase 3 study was performed to evaluate the effectiveness of ofatumumab in patients with bulky fludarabine-refractory chronic lymphocytic leukaemia (BFR CLL) as compared to physician’s choice. The five-year follow-up of this phase 3 trial showed that ofatumumab therapy resulted in a numerically but not significantly longer overall survival. As only few patients had the chance to receive a kinase inhibitor later, the study displays the survival of BFR CLL patients in the period prior to receiving small-molecule inhibitors. Ofatumumab is a well-tolerable treatment option in multiresistant advanced CLL.

Keywords: ofatumumab, physician choice, chronic lymphocytic leukaemia.
Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia, with an age-adjusted incidence of 4–5 per 100,000 people in Western countries (Hallek et al., 2018). Results of the GCLLSG trial suggested that approximately 20% of patients become refractory to fludarabine-based therapy and cease to respond to or progress within six months of a fludarabine-containing therapy (Hallek et al., 2010). Around 30–40% of fludarabine-refractory patients showed bulky lymphadenopathy (one or more lymph nodes >5 cm in the greatest dimension) (Eketorp et al., 2014). Patients with bulky lymphadenopathy were significantly more likely to exhibit disease progression than those without. Moreover, although bulky lymphadenopathy is associated with 11q deletion, CLL patients with other chromosomal abnormalities (e.g. trisomy 12 or 17p deletion) may also present with bulky lymphadenopathy.

During the initial treatment phase of CLL patients, adding anti-CD20 therapy such as rituximab to fludarabine-based chemotherapy showed better efficacy in terms of progression-free survival (PFS) and overall survival (OS) versus chemotherapy alone. However, one-third of patients from both groups experienced significant treatment resistance, which was correlated with poor OS (Zenz et al., 2010).

Ofatumumab (OFA), a type I, fully human immunoglobulin (IgG1k) antibody, binds to a different epitope of the CD20 cell surface antigen, which is closer to the cell membrane, redistributes CD20 into lipid rafts, binds more avidly to CD1q (the first component of the complement cascade) and has a slower off-rate compared with rituximab (Teeling et al., 2004; Teeling et al., 2006; Pawluczkwycz et al., 2009). In a previous non-randomised study, treatment with single-agent ofatumumab showed an OS of 17.3 months in fludarabine- and alemtuzumab-refractory patients with CLL (Teeling et al., 2004). The overall response rate (ORR), which was the primary endpoint, was 58% and 47% in the fludarabine- and alemtuzumab-refractory group and bulky fludarabine-refractory (BFR) group, respectively (Wierda et al., 2010a).

In 2014, a planned interim analysis of an open-label, two-armed, randomised, phase III study comparing ofatumumab with treatment of physicians’ choice (PC) (most patients received rituximab-, alemtuzumab-, alkylator-, or fludarabine-based therapies) in patients with BFR CLL was conducted to assess the effectiveness of ofatumumab during the time period prior to the availability of small-molecule kinase inhibitors. The study did not meet its primary endpoint of PFS, as assessed by an independent review committee [median PFS: 5.4 vs. 3.6 months for ofatumumab vs. physicians’ treatment choice; hazard ratio (HR) = 0.79, 95% confidence interval (CI): 0.50, 1.24; P = 0.268] (Österborg et al., 2016). Here we report the five-year survival follow-up from the same study.

**Patients and methods**

Patients with BFR CLL were stratified based on 17p deletion status, the Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2) and fludarabine-refractory status (no response or less than six months response), and were randomised (2:1) to receive either ofatumumab or physicians’ choice of therapy. Patients in the ofatumumab arm received an initial dose of 300 mg, which was followed one week later with 2000 mg once weekly for seven weeks, further followed four weeks later by one infusion of 2000 mg every four weeks for four consecutive infusions, adding to a total of 12 infusions over 24 weeks. Patients in the physicians’ choice arm received non-ofatumumab-based regimens permitted for CLL and standard-of-care regimens for up to six months. After 24 weeks, patients enrolled in the ofatumumab arm achieving at least stable disease or better were further randomised (2:1) to either an ofatumumab-extended arm (additional dose regimen of 2000 mg once every four weeks up to 24 weeks) or an observation arm (no further therapy). Patients from the physicians’ choice arm who received ofatumumab after experiencing progressive disease (PD) had an option to receive single-agent ofatumumab therapy in the salvage arm (cross-over). All patients were required to provide written informed consent. The study protocol was approved by the institutional review board or ethics committee at each participating centre, and the study was conducted in accordance with the Declaration of Helsinki.

The primary aim of this five-year follow-up report was to analyse OS after five years of follow-up, along with presentation of the cumulative safety data. All data up to the time of withdrawal are included in the analysis.

OS was defined as the interval of time (in months) between the date of randomisation and the date of death due to any cause. Survival distributions of OS were estimated using the Kaplan–Meier method. A stratified Cox regression model along with two-sided 95% CI was used to estimate HR of OS.

**Results**

Patients with a median age of 61.5 and 63 years received a median of six and three treatment cycles in the ofatumumab and physicians’ choice arms, respectively. The interim analysis of PFS has been presented earlier (Österborg et al., 2016). After 24 weeks of ofatumumab treatment, patients continuing therapy underwent a second 2:1 randomisation (24 continued ofatumumab in the extended arm and 13-stopped ofatumumab in the observation arm). Of the 43 patients randomised to the physicians’ choice arm for up to six months, 22 received ofatumumab salvage therapy at PD. Almost equal proportions of patients completed study treatment in the ofatumumab (76%) and physicians’ choice (77%) arms. Adverse events (AEs) were the most common reason for study treatment discontinuation and were comparable between the ofatumumab (24-week group and extended-therapy group) and physicians’ choice (13% vs. 12%) arms.
Median OS was 19.2 months vs. 14.5 months in the ofatumumab and physicians’ choice arms, respectively (HR = 0.75, 95% CI: 0.48, 1.17; P = 0.173, stratified log-rank test). The estimated median OS for the ofatumumab-extended arm was 31.5 months (Fig 1). There was no significant difference in OS between the ofatumumab-extended and physicians’ choice arms (P = 0.102).

Investigator-assessed ORR for the ofatumumab and physicians’ choice arms remained unchanged from the interim analysis (49% vs. 37%, respectively). However, in the ofatumumab salvage arm (55%), a 5% increase in investigator-assessed ORR was noted in comparison with that reported in the previous analysis (50%).

Most common AEs in the ofatumumab and physicians’ choice arms (>15% in either) were neutropenia (21% vs. 19%, respectively), pneumonia (18% vs. 19%) and anaemia (9% vs. 19%). Grade 3, 4 and 5 AEs (>10%) included neutropenia (17% vs. 16%), pneumonia (14% vs. 9%), febrile neutropenia (9% vs. 12%) and anaemia (6% vs. 14%). Serious AEs (≥5%) included pneumonia (13% vs. 16%), febrile
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Osterborg et al., 2016; van Oers et al., 2015) have demonstrated
longer OS with the use of low-dose maintenance CD20 mAb
therapy, a finding that may be re-explored in the new,
high-cost targeted therapeutic landscape for CLL. Ofatumumab is
a safe treatment option but with moderate activity in cases
with multi-drug-resistant advanced CLL.

**Table I. Post-treatment anti-cancer therapy administered.**

| Type of anti-cancer therapy | OFA arm | PC arm | Total |
|-----------------------------|---------|--------|-------|
| Any anti-cancer therapy, n (%) | (n = 79) | (n = 43) | (n = 122) |
| Yes | 44 (56) | 8 (19) | 52 (43) |
| No | 35 (44) | 35 (81) | 70 (57) |

OFA, ofatumumab; PC, physician’s choice.

*Includes ibrutinib and idelalisib.

Table I. Post-treatment anti-cancer therapy administered.

| Type of anti-cancer therapy | OFA arm | PC arm | Total |
|-----------------------------|---------|--------|-------|
| Monoclonal antibodies | 26 (33) | 8 (19) | 34 (28) |
| Chemotherapy | 37 (47) | 5 (12) | 42 (34) |
| Corticosteroids | 20 (25) | 6 (14) | 26 (21) |
| Small-molecule targeted therapy* | 11 (14) | 3 (7) | 14 (11) |

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**Author contributions**

Data analysis and interpretation were performed by TS, VS, GV, AO, GM, SG* and MU. Collection and assembly of data were performed by SG, IK, GR and AO. Concept and design were undertaken by AO and MU. TS, VS, GV, SG, MM, GR, AO, GM and MU contributed to manuscript writing. CL, TS, IK, VS, GV, SG, MM, GR, AO, GM and MU contributed to final approval of the manuscript and are accountable for all aspects of the work (ensuring questions related to accuracy or integrity of the work are appropriately investigated and resolved). SG*, Sameera Govindaraju.

**Conflicts of interest**

TS and GV are employed by and hold stock or other ownership of Novartis. SG* is employed by Novartis. IK has consulting or advisory roles with Takeda and Janssen, received research funding from Novartis, Janssen, MSD, Bayer, provided expert testimony on behalf of Takeda, Janssen and Roche and received travel, accommodation or expenses from Takeda, Janssen, MSD, Roche and AbbVie. VS is employed by Eco-safety Medical Centre, owns stock and other ownership of AbbVie, Bristol-Myers Squibb, JUNO, Pfizer, Gilead, Portola, Ignyta and Kite, received research funding from Janssen and accepted travel, accommodation or expenses
tyrosine kinase and other mutations have started to appear. Thus, agents such as mAbs, in particular those that may not exhaust effector functions, may remain useful as part of the total therapy concept for CLL.

In conclusion, the five-year follow-up of this phase III trial showed a numerically longer, although not statistically significant, median OS (+4-7 months) in the ofatumumab arm with an estimated median OS of 19-2 (vs. 14-5 months in the PC arm). However, the estimated median OS of the OFA extended arm was 31-5 months. Thus, the longer OS observed at five-year follow-up appears to be driven by those receiving extended ofatumumab therapy. Since only a few patients had the opportunity to receive a bruton kinase inhibitor later, the study displays the survival of BFR CLL patients during the period before the administration of small-molecule inhibitors (Table I). This study and others (Zenz et al., 2010; van Oers et al., 2015) have demonstrated longer OS with the use of low-dose maintenance CD20 mAb therapy, a finding that may be re-explored in the new, high-cost targeted therapeutic landscape for CLL. Ofatumumab is a safe treatment option but with moderate activity in cases with multi-drug-resistant advanced CLL.

**Discussion**

In the present five-year follow-up study, median OS was 4-7 months longer in the ofatumumab arm (19-2 months) versus the physicians’ choice arm (14-5 months), but the difference was not significant. In a planned interim analysis of a large multicentre trial of single-agent ofatumumab use in patients with fludarabine-refractory and BFR CLL respectively, OS was 13-7 and 15-4 months, and the final analysis presented a median OS of 14-2 and 17-4 months (Wierda et al., 2010a, 2010b), which is in line with the current report.

In the present study, a higher number of patients (56%) in the ofatumumab arm, and 19% of patients in the PC arm received post-study treatment anti-cancer therapy. These treatments included monoclonal antibodies (mAbs) (33% vs. 19%), chemotherapy (47% vs. 12%), corticosteroids (25% vs. 14%) and targeted therapies (ibrutinib, idelalisib, etc.) (14% vs. 7%) in the ofatumumab vs. physicians’ choice arms, respectively.

In conclusion, the five-year follow-up of this phase III trial showed a numerically longer, although not statistically significant, median OS (+4-7 months) in the ofatumumab arm with an estimated median OS of 19-2 (vs. 14-5 months in the PC arm). However, the estimated median OS of the OFA extended arm was 31-5 months. Thus, the longer OS observed at five-year follow-up appears to be driven by those receiving extended ofatumumab therapy. Since only a few patients had the opportunity to receive a bruton kinase inhibitor later, the study displays the survival of BFR CLL patients during the period before the administration of small-molecule inhibitors (Table I). This study and others (Zenz et al., 2010; van Oers et al., 2015) have demonstrated longer OS with the use of low-dose maintenance CD20 mAb therapy, a finding that may be re-explored in the new, high-cost targeted therapeutic landscape for CLL. Ofatumumab is a safe treatment option but with moderate activity in cases with multi-drug-resistant advanced CLL.

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**Author contributions**

Data analysis and interpretation were performed by TS, VS, GV, AO, GM, SG* and MU. Collection and assembly of data were performed by SG, IK, GR and AO. Concept and design were undertaken by AO and MU. TS, VS, GV, SG, MM, GR, AO, GM and MU contributed to manuscript writing. CL, TS, IK, VS, GV, SG, MM, GR, AO, GM and MU contributed to final approval of the manuscript and are accountable for all aspects of the work (ensuring questions related to accuracy or integrity of the work are appropriately investigated and resolved). SG*, Sameera Govindaraju.

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from AbbVie and Janssen. MM has an Honoraria from Abb-Vie, Janssen, Gilead and Roche, has a consulting or advisory role with AbbVie, Janssen, Gilead and Astra Zeneca; is in the speakers’ bureaus of AbbVie, Janssen and Gilead, and has received research funding from Roche. AO’s institution accepted research funding from AbbVie, Gilead and Janssen.

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