Economic Analysis of Alemtuzumab (MabCampath®) in Fludarabine-refractory Chronic Lymphocytic Leukemia

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Abstract: Objective: The objective of this economic analysis is to determine the cost-effectiveness of alemtuzumab in the treatment of B cell chronic lymphocytic leukemia (B-CLL) patients who have progressed despite fludarabine therapy.

Method: This model was developed according to the Canadian public payer health system considering only direct medical costs. Effectiveness information was obtained from the published literature. Resource utilization was based on guidelines, literature and expert opinion. Cost information was obtained from provincial costing sources and presented in 2008 Canadian dollars. The primary comparators for this analysis were alemtuzumab, Various Treatments (VT) (combination of agents), fludarabine+cyclophosphamide (FC), fludarabine+cyclophosphamide+rituximab (FCR) and best supportive care (BSC).

Results: Estimated mean survival for alemtuzumab was 22.68 months (1.89 years). Mean survival for VT was estimated from the literature at 16.32 months (1.36 years). The mean survival for FC was 17.44 months (1.45 years) and FCR 20.06 months (1.67 years). The incremental cost-effectiveness ratio (ICER) for alemtuzumab vs VT was $43,615/LYG; $52,536/LYG for the alemtuzumab vs FC; $21,818/LYG vs FCR; and less costly and more effective vs BSC. ICERs were sensitive to three variables: treatment duration of alemtuzumab; treatment duration of FCR; and additional survival due to rituximab for FCR patients compared to FC.

Conclusion: The results showed that the ICERs for alemtuzumab in B-CLL patients who have failed fludarabine ranged from $21,818/LYG to $52,536/LYG compared to active treatment, and was less costly and more efficacious compared to BSC.

Keywords: Alemtuzumab, chronic lymphocytic leukemia, cost-effectiveness, economic analysis, fludarabine.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a type of leukemia resulting from an abnormal neoplastic proliferation of B-lymphocytes. The B-lymphocytes accumulate in the bone marrow, blood, lymph glands and spleen [1]. CLL is the most common adult leukemia with an incidence of 3 per 100,000 populations. The median age of onset is 65 to 70 years of age [2]. Clinical features include elevated white blood cells, lymphocytosis, lymphadenopathy, splenomegaly, fatigue, fever, anemia and infection.

The natural history of CLL is variable, but median overall survival has been estimated to exceed 10 years in patients who are diagnosed in early stages [3]. CLL is incurable and is treated when patients become symptomatic. Treatment is required for patients who develop symptomatic splenomegaly or lymphadenopathy, hemolytic anemia or a decline in hemoglobin or platelet count to unacceptably low levels [4]. Alkylator chemotherapies (chlorambucil and cyclophosphamide) and fludarabine are the mainstay of therapy [5]. For those who cannot be controlled by fludarabine, the prognosis is poor. An estimated 40% of fludarabine-refractory patients survive beyond 12 months [6]. According to literature, there is no standard treatment for fludarabine refractory patients. A variety of treatments [Various Treatments (VT)] might be used, including novel therapies available on clinical trials, immuno-modulatory e.g., lenalidomide, pulse corticosteroids, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone), or fludarabine again (often in combination with immuno-chemotherapy).

Alemtuzumab is a humanized antibody that binds to the CD52 antigen expressed on peripheral blood lymphocytes, monocytes and macrophages [7]. Alemtuzumab is indicated for the treatment of CLL in patients who have been treated with alkylating agents and whose CLL has progressed despite fludarabine therapy [7]. Majority of the evidence in CLL is based on non-randomized clinical studies [6, 8-21]. The pivotal alemtuzumab publication by Keating and colleagues investigated the efficacy and safety of alemtuzumab in patients (N=93) with refractory or relapsed CLL.
Alemtuzumab is more expensive compared to other active treatments for fludarabine-refractory patients but may offer some improved efficacy. Consequently, determination of the cost-effectiveness of alemtuzumab was warranted. One published economic evaluation of alemtuzumab in CLL was found [23]. In that study, intravenous alemtuzumab was compared to FCR in refractory CLL. Direct costs from New Zealand were used in the conduct of a cost-minimization analysis. Costs were presented in 2006 New Zealand dollars (SNZ1.00 = SCAD0.80 [24]). Total direct medical cost was SNZ 50,311 for alemtuzumab and SNZ 65,613 for FCR. An ICER was not presented since both survival and quality-of-life were assumed to be equivalent for both groups.

METHODS

The perspective of the analysis was that of the Canadian public payer health system.

The choice of comparator for alemtuzumab was complex because 1) there is no comparative study for alemtuzumab patients who were fludarabine-refractory or relapsed patients and 2) 3rd line treatment is not standardized and thus consists of a number of treatments. Two recently published clinical guideline documents discussed only first and second-line therapies [11, 25]. For this analysis, comparators consisted of alemtuzumab, VT, fludarabine+cyclophosphamide (FC), fludarabine+cyclophosphamide+rituximab (FCR), and best supportive care (BSC) based on literature, guidelines and expert opinion. For VT therapy in CLL, purine analogs, including fludarabine, based treatment was the most common treatment reported (78%) in the Keating study of VT therapy in CLL [26]. Purine analogs were the most commonly reported agents (single agent was reported by 22%; combined with another agent in 56%). Consequently, this economic analysis used fludarabine as a surrogate for VT therapy and as such the cost of treatment with FC was used as a surrogate for VT.

A comprehensive review of literature for clinical outcomes for alemtuzumab, FC, FCR, VT and BSC was conducted to determine overall survival time. Several search strategies were used to comprehensively collect and examine appropriate clinical data for this economic evaluation, including formal MEDLINE searches; Consensus panel; Cancer Care Ontario; Other sources/bibliographies. For MEDLINE, since 3rd line treatment after fludarabine is a “mish mash” of treatments a search of CLL, salvage, fludarabine, refractory (1996-present-2nd week March 2008) was conducted. Only studies limited to the English language and human subjects, categorized as clinical trials, were included. Appropriate citations to review included original studies examining the efficacy and safety of treatment in CLL patients who were fludarabine-refractory.

All studies reported survival in terms of median survival. Mean survival values were obtained from a number of sources: raw data from published sources and digital mapping based on published sources. A number of clinical studies have examined the efficacy and safety of alemtuzumab in CLL patients (Table 1). The Keating study was considered the pivotal study with a sample size of 93 patients enrolled and almost 50% of patients had a severe Rai stage [22]. Hui and colleagues reported that alemtuzumab led to a median overall survival of 15.1 months [13]. The retrospective cohort study examined the efficacy and safety of patients prescribed alemtuzumab for CLL in a population of patients who had experience with fludarabine and 72% were considered refractory. Two other studies examined the efficacy of intravenous alemtuzumab fludarabine-refractory patients, Rai [9] (N=24) and Fiegl [16] (N=115). Stilgenbauer and colleagues conducted a phase II study of subcutaneous alemtuzumab in fludarabine-refractory patients (N=109) [10]. That publication was the preferred source for clinical outcome information for this economic evaluation because it was the most recently published and was based on a large (N=103) CLL dataset. There were no direct studies comparing alemtuzumab to VT therapy, FC, or FCR in a fludarabine-refractory CLL population. Table 2 summarizes VT, FC and FCR studies in a population of fludarabine-refractory CLL. The O’Brien, 2001 study was chosen to represent the FC comparator over the Weirda, 2006 study because it had a higher quality study design, namely it was a prospective study compared to a retrospective study. Moreover, the population in Weirda, 2006 study was taken from a clinical trial database that had collected data from the O’Brien, 2001 study. Consequently, the O’Brien, 2001 study was the original research.

For resource utilization, the FCR treatment protocol used in this economic evaluation was based on the methodology from the FCR study [12], guidelines for FC in CLL [28], rituximab in non-Hodgkin’s lymphoma (NHL) [29], and rituximab in CLL [30]. BSC data for resource utilization were obtained from published literature examining the costs of palliative care in Canada [31].

All costs were presented in 2008 Canadian dollars. Unit costs were multiplied by health care resources, namely medication use, medication administration, adverse events, utilized by the patients in order to determine the total cost of variables. Treatment cost represented one course of treatment. All drug costs were based on the Ontario Drug Benefit Formulary/Comparative Drug Index unless otherwise stated [32]. Alemtuzumab is available for intravenous (IV) and subcutaneous (SC) administration but it was assumed that most patients would utilize the SC form due to convenience and self-administration. 83% of patients included in an observational cohort in British Columbia utilized the SC form [13] and thus costs were weighted 83% SC and 17% IV. The cost of alemtuzumab was based on twelve cycles with three treatments per cycle. In the present economic evaluation, the dose of rituximab was fixed at 375 mg/m².

Other costs included physician visits, monitoring, laboratory tests, and prophylaxis. Prophylaxis was based on Cancer Care Ontario utilization information for each agent [28, 33, 39]. Resources for administering agents were based on Ontario guidelines. Thrombocytopenia and neutropenia costs were based on a study of NHL patients who were treated with fludarabine [35]. The rate of CMV infection/reactivation and all grade III and IV adverse drug reactions for alemtuzumab was based on the Stilgenauer study. Cost of a CMV consisted of an additional hematologist visit ($64.05 per visit, OHIP A613). A
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published CMV treatment guideline recommended valganciclovir as prophylaxis and ganciclovir or valganciclovir for treatment of CMV [44]. Treatment guidelines for alemtuzumab recommended famciclovir or equivalent as prophylaxis [39]. It was, therefore, assumed that patients would continue famciclovir, rather than switch to an alternative guanine analog. The medication cost for CMV is therefore included in the prophylaxis cost. PCR blood tests are recommended by guidelines to monitor patients for CMV infections. However, PCR blood test costs were not included in the analysis since the tests were not covered by the Ontario health care system. Cost of treating a rash consisted of four weeks treatment with: topical clindamycin 2% ($0.862); hydrocortisone 1% lotion ($0.1462); oral minocycline 100mg twice daily ($1.0332 per 100mg) [34]. Cost of nausea/vomiting and neutropenia were based on a study of non-Hodgkin’s lymphoma patients treated with fludarabine [35]. Grade III and IV fever or infections from the FC study were assumed to be neutropenia.

The incremental cost-effectiveness ratio (ICER), where the incremental cost per life-year-gained (LYG), was the primary outcome of the analysis. To test the robustness of the results, one-way sensitivity analyses were conducted with regard to variations in key parameters (efficacy, adverse events, resource utilization parameters and costs).

RESULTS

Examination of the alemtuzumab and comparator studies showed that patients in the alemtuzumab studies included a higher proportion of patients with refractory disease and higher Rai scores but were generally similar with respect to age and gender, indicating that the alemtuzumab patients were potentially sicker than the comparator patients, thus biasing against alemtuzumab.

Median overall survival (OS) was presented as the outcome in each of the studies (Table 3). However, mean OS was required for the economic evaluation. In order to obtain the mean value, digitization was used to determine mean OS.
values for alemtuzumab, FC and VT (labelled as salvage therapy) as requests for access to raw data or mean OS were not successful (Fig. 1 and Table 3). In addition, the mean OS for FCR was obtained by multiplying mean OS for FC by a factor of 15% representing the theoretical benefit of adding rituximab to FC [5]. This method provided the best estimate of efficacy for a comparator given the non-comparative literature available and the lack of patient level data available.

Table 2. Summary of Comparators

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<tr>
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<tbody>
<tr>
<td>Treatment</td>
<td>VT therapy</td>
<td>FCR</td>
<td>FC</td>
<td>F, FC and FCR</td>
</tr>
<tr>
<td>Number of patients</td>
<td>147</td>
<td>177</td>
<td>128</td>
<td>F=251</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FC=111 FCR=143</td>
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<tr>
<td>Type of study</td>
<td>Retrospective American database</td>
<td>Prospective open label trial</td>
<td>Prospective open label trial</td>
<td>Retrospective American database</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FC: 59 [31, 79]</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>FCR: 58 [36, 81]</td>
</tr>
<tr>
<td>Sex, N (proportion) males</td>
<td>113 (0.77)</td>
<td>131 (0.74)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Fludarabine failure/refractory</td>
<td>Refractory: 147 (1)</td>
<td>Refractory (did not achieve PR or progression within 6 months): 37 (0.21) Sensitive: 108 (0.61)</td>
<td>28 (0.22)</td>
<td>Resistant F: 0</td>
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<td></td>
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<td></td>
<td></td>
<td>FC: 26 (0.23)</td>
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<td></td>
<td></td>
<td>FCR: 20 (0.14)</td>
</tr>
<tr>
<td>Performance status, N (proportion)</td>
<td>Status 0: 21 (0.14)</td>
<td>Status 0: 22 (0.12)</td>
<td>Status 0: 22 (0.12)</td>
<td>Status 0: 21 (0.14)</td>
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<td></td>
<td>Status 1: 101 (0.69)</td>
<td>Status 1: 145 (0.82)</td>
<td>Status 1: 145 (0.82)</td>
<td>Status 1: 101 (0.69)</td>
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<td>Status 2: 25 (0.17)</td>
<td>Status 2: 10 (0.06)</td>
<td>Status 2: 10 (0.06)</td>
<td>Status 2: 25 (0.17)</td>
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<tr>
<td>Number of prior CLL treatments, median [range]</td>
<td>3 [1, 8]</td>
<td>2 [1, 10]</td>
<td>1 [0, 7]</td>
<td>1 to 2 regimens F: 138 (0.55)</td>
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<td></td>
<td>FC: 77 (0.69)</td>
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<td></td>
<td>FCR: 102 (0.71)</td>
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<td>≥3 regimens F: 113 (0.45)</td>
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<td></td>
<td></td>
<td>FC: 34 (0.31)</td>
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<td></td>
<td></td>
<td>FCR: 41 (0.29)</td>
</tr>
<tr>
<td>Rai stage, N (proportion)</td>
<td>0 to 2: 47 (0.32)</td>
<td>89 (0.50)</td>
<td>68 (0.53)</td>
<td>Stage 1 to 2 F: 93 (0.37)</td>
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<td></td>
<td>FC: 51 (0.46)</td>
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<td></td>
<td>FCR: 63 (0.44)</td>
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<td>3: 28 (0.19)</td>
<td>23 (0.13)</td>
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<td>4: 72 (0.49)</td>
<td>65 (0.37)</td>
<td>Stage 3 to 4 F: 146 (0.58)</td>
<td>Stage 3 to 4</td>
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<td></td>
<td>FC: 56 (0.50)</td>
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<td></td>
<td></td>
<td>FCR: 76 (0.53)</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td>Median OS</td>
<td>Median OS: 42 months</td>
<td>Median OS: 52 months</td>
<td>Median OS:</td>
</tr>
<tr>
<td>ALK refractory: 8 months</td>
<td>OR: 101 (0.57)</td>
<td>OR: 101 (0.57)</td>
<td>Prior ALK therapy: 38 months</td>
<td>F: 20 months</td>
</tr>
<tr>
<td>ALK-sensitive: 14 months</td>
<td>CR: 44 (0.25)</td>
<td>CR: 44 (0.25)</td>
<td>Prior ALK+F therapy: 21 months</td>
<td>FC: 31 months</td>
</tr>
<tr>
<td>ALK naïve: 10 months</td>
<td>PR: 57 (0.32)</td>
<td>PR: 57 (0.32)</td>
<td>Prior F therapy: 12 months</td>
<td>FCR: 49 months</td>
</tr>
<tr>
<td>OR: 32 (0.22)</td>
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<td>CR: 2 (0.01)</td>
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ALK = alkylating agent; CR = complete response; F = fludarabine; FC = fludarabine and cyclophosphamide; FCR = fludarabine, cyclophosphamide and rituximab; OR = overall response = CR + PR; OS = overall survival; PFS = progression free survival; PR = partial response.
Hematologic (e.g., infection, neutropenia, febrile neutropenia) and opportunistic infections (e.g., cytomegalovirus (CMV) rates and reactivations) were considered. Resource utilization for only grade III and IV adverse drug reactions (ADRs) were considered as Grade I and II ADRs would be resolved with minimal or no direct costs and no protocol for the treatment of grade I or II ADR exists, thus adding to the difficulty in attributing a representative cost. The cost of BSC equaled the cost of palliative care at $34,411.

Fig. (1). Survival curves for alemtuzumab, FC and Various Treatments.

Overall costs included in the analysis were drug acquisition, prophylaxis, administration, monitoring and costs due to adverse drug events (Table 4).

Using digitized mean OS (Fig. 1), the ICERs ranged from dominant situation for BSC (lower cost and better outcome for alemtuzumab) to $52,536 per LYG (alemtuzumab vs FC) to $28,896/LYG (alemtuzumab vs FCR) (Table 5).

**Sensitivity Analysis**

Sensitivity analyses for the various comparative groups were conducted. The acquisition cost of alemtuzumab accounted for the largest proportion of the total alemtuzumab treatment protocol cost. In general, changing the proportion of IV use and increasing CMV rate had minimal impact on the ICERs for all comparisons.

The ICER was sensitive to three variables. First, decreasing the number of alemtuzumab cycles from 12 to 8 resulted in ICERs of $34,807/LYG (alemtuzumab vs FC); dominant for alemtuzumab vs FCR (less costly and more effective); $28,896/LYG (alemtuzumab vs VT). Second, varying the number of FCR cycles resulted in an ICER of $55,564/LYG for 4 FCR cycles, and alemtuzumab dominating FCR for 8 FCR cycles. Third, varying the additional benefit of rituximab compared to FC between 10% and 20% resulted in ICERs for alemtuzumab vs FCR of $16,473/LYG and $32,870/LYG respectively.

**DISCUSSION**

Monoclonal antibodies represent a novel approach to cancer treatment in prognosis poor fludarabine-refractory CLL patients. However, the quality of evidence for alemtuzumab in 3rd line therapy is not high. A comprehensive review of CLL interventions indicated similar patient populations in terms of diagnosis, severity and number of prior treatments. Only two comparative studies of alemtuzumab were found. One study closed early due to adverse events [36] and another study was conducted in an untreated patient population [37]. Clinical evidence obtained from non-comparative data is not optimal for the conduct of economic evaluations. However, given the lack of comparative data available, non-comparative data was the best level evidence available for this economic analysis of a fludarabine-refractory target population. No studies directly comparing alemtuzumab to VT therapy, FC or FCR were found. Non-comparative studies of FC, FCR and VT therapies existed. There is some question as to the appropriateness of using FC or FCR as comparators. Some of the non-comparative studies treated fludarabine-refractory CLL patients with fludarabine again, perhaps biasing the result in that previous non-responders may not respond well a second time. The decision to use FC and FCR as comparators was based on literature and expert opinion where fludarabine refractory patients were given FC and FCR [27].
The OS curves are based on three separate studies in CLL. Due to possible differences in study design and treatment protocols, patients and studies may not be directly comparable. Published studies directly comparing treatments of interest were not available. Areas under the published survival curves for alemtuzumab, FC and VT was used to estimate mean OS. Requests for access to raw data or overall survival values from the investigators of the published studies were not successful.

The mean OS for FCR was based on the FC survival estimate multiplied by a theoretical estimate of the benefit due to the addition of rituximab [5]. It is important to note that publications did not examine the impact of rituximab on FC in a fludarabine-refractory population. The method provided the best estimate of efficacy of FCR given the non-comparative literature and the lack of patient level data. It is important to note that one randomized trial of FCR versus FC was found [38]. However, results from the Robak study were not considered in the economic analysis due to the trial's target population, namely patients who were sensitive to fludarabine. In contrast, fludarabine-refractory patients were included in the alemtuzumab (72% in Hui [13], and 100% in Stilgenbauer [10]), FC (22%) [6] and VT therapy (100%) [26].

At higher OS values for FCR, FCR would be the dominant scenario vs alemtuzumab. However, there are no data to support such improved outcomes associated with rituximab for the fludarabine-refractory target population.

The base case analysis used an intravenous to subcutaneous administration ratio of 17%:83%. This ratio was based on the ratio reported in a Canadian study [13]. The actual ratio of intravenous to subcutaneous use of alemtuzumab in Ontario was determined through a formal unpublished survey in Ontario. Results showed that in 2007, out of 24 patients, 2 patients were administered both SC and IV, while the remaining 22 patients were administered SC alone. This ratio showed that there was little intravenous use in Ontario. The base case, with its higher IV utilization rate,
is conservative as it would result in higher costs for drug administration for alemtuzumab.

CLL patients are predisposed to infections even in the absence of treatment. With alemtuzumab the rate of grade III/IV infections was 27% [22]. Lin and colleagues administered filgrastim to CLL patients (N=14) in order to decrease the rate of infection associated with alemtuzumab treatment [41]. Filgrastim 5ug/kg was administered subcutaneously 5 days prior and throughout the 12 week alemtuzumab IV therapy. Study patients were considered quite ill. All but one patient was fludarabine-refractory. Patients had received a median of 3.5 prior treatment medications. More than half of the patients were defined as Rai stage III/IV. In terms of response, only four patients (28.6%) actually completed treatment and only three achieved a partial response. Nine out of 14 patients discontinued treatment due to CMV reactivation or neutropenia. Eleven patients developed grade 3 anemia. In terms of opportunistic infections, 43% of patients (6/14) developed CMV reactivation. Anti-viral prophylaxis was not reported in the study. Infusion related reactions were minimal. Three deaths (21.4%) were reported. Results showed that the addition of filgrastim did not decrease the rate of infection in patients receiving alemtuzumab and that the combination of alemtuzumab and filgrastim was not recommended as therapy.

Opportunistic infection rates and reactivation rates associated with alemtuzumab are of concern. A review of the included studies utilized in this economic evaluation showed that CMV reactivation rates ranged from 7 to 13% in the alemtuzumab studies [10, 13, 16, 22]. Those study protocols provided antiviral agents as prophylaxis. The overall opportunistic infection rates were much higher (42%) in one study where antiviral prophylaxis was not provided [9].

Rituximab is a chimeric monoclonal antibody for CD20. Rituximab has been shown to be active in a number of B-cell lymphomas [40, 42]. The addition of rituximab to standard fludarabine has been shown to prolong the OS in previous untreated CLL patients [5]. This economic analysis is based on the assumption that there was a 15% increase in OS associated with rituximab in addition to FC. Consequently, the method provided the best estimate of efficacy for a comparator given the non-comparative literature available and the lack of patient level data available. This assumption was tested in a sensitivity analysis. It is important to note that alemtuzumab+fludarabine is being compared to fludarabine alone in an ongoing industry sponsored randomized phase III study.

It is important to note, that while this economic analysis was being conducted, there was another publication by Fiegl and colleagues (2010), examining the effectiveness of alemtuzumab in a CLL population [43]. Results from that study showed a median OS in the total cohort and in 17p-deleted patients was 32.8 and 19.1 months, respectively based on a retrospective cohort of European CLL patients. The efficacy results are much greater than previously shown (Table 1). A review of the cohort included in the Fiegl 2010 publication showed relatively similar demographics and an overlap of population from the Fiegl 2006 population [16, 43]. As a conservative option, we chose to incorporate the more recent Stilgenbauer results as they were in-line with other previous alemtuzumab publications as the large increase in median OS would translate into a mean OS of >2 years.

CONCLUSION

Alemtuzumab is indicated for the treatment of B-CLL in patients who have been treated with alkylating agents and who have failed fludarabine therapy. There is a paucity of comparative studies for alemtuzumab and thus a number of assumptions regarding comparators were made, leading to uncertainty. Based on the available data, we show that alemtuzumab in B-CLL patients who have failed fludarabine ranged from $21,818/LYG to $32,536/LYG depending on the comparator compared to active treatment, and was less costly and more efficacious compared to BSC.

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Declared none.

DECLARATION OF INTERESTS

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