Lundin *et al.* [15] reported CMV reactivation in 4 patients (11%) treated with subcutaneous alemtuzumab. One case of PCP occurred in a patient not receiving prophylaxis. An update describing the long-term follow-up for that patient cohort documented 1 episode of symptomatic Epstein–Barr virus (infection 21 months post alemtuzumab therapy) [16]. No other serious infections occurred.

Alemtuzumab in Combination with Additional Agents for Relapsed or Refractory CLL: Faderl *et al.* [17] documented infections in 52% of patients with lymphoid malignancies treated with alemtuzumab in combination with rituximab; CMV reactivation occurred in 27%. Infections in CLL patients were not reported separately.

Elter [19] reported data on 36 patients treated with alemtuzumab in combination with fludarabine; fungal pneumonia ($n = 2$), CMV reactivation ($n = 2$), and infection-related death ($n = 1$ case of *Escherichia coli* sepsis) were the only reported infection-related complications.

Wierda *et al.* [18] reported CMV reactivation in 24% of patients ($n = 21$) treated with alemtuzumab in combination with cyclophosphamide, rituximab, and fludarabine.

Alemtuzumab Consolidation for Patients with a Response to Previous-Line Therapy: Wendtner *et al.* [20] randomized patients with a response to first-line fludarabine-containing chemotherapy to consolidation with alemtuzumab (30 mg intravenously 3 times weekly for 12 weeks) or observation. Explicit stopping rules were determined *a priori* and included grade 3 or 4 infection occurring in 5 of the first 10 patients accrued to the alemtuzumab arm. The study was stopped early because of severe infections in 7 of 11 patients randomized to alemtuzumab consolidation. Grades 3 and 4 infections included CMV reactivation ($n = 2$), CMV pneumonitis ($n = 2$), pulmonary aspergillosis and HSV/human herpes virus 6 ($n = 1$), pulmonary tuberculosis ($n = 1$), and herpes zoster reactivation ($n = 1$). An additional 2 patients developed grade 2 CMV reactivation. Overall, 9 of 11 patients (82%) randomized to alemtuzumab consolidation discontinued therapy because of an adverse event (severe infection in 5 patients and severe myelosuppression in 4 patients).

Four additional single-arm studies reported infection-related toxicity for alemtuzumab consolidation therapy [22–25]. Reactivation of CMV was common, occurring in 21%–57% of patients; the single reported case of CMV pneumonitis [22] contributed to patient death. The studies evaluated either a 10-mg or 30-mg dose of alemtuzumab administered over 6 to 8 weeks. No apparent difference in the rate or severity of infections by treatment regimen was observed.

4.2.3 Question 3

Which patients are more likely—or less likely—to benefit from treatment with alemtuzumab?

Statistical evaluations for independent predictors of response, response duration, or survival were not reported in any study—including in the present systematic review. However, several publications reported subgroup analyses and clinical observations for patients who were more or less likely to respond to alemtuzumab.

Several authors noted that patients with lymphadenopathy, particularly bulky lymph nodes (>5 cm), were less likely to achieve a clinical response to alemtuzumab-containing therapy [5,7,11,12,15,20,23]. Keating *et al.* [5] reported that patients less likely to respond included those with Rai stage IV disease, with at least 1 lymph node greater than 5 cm in diameter, or with a World Health Organization (WHO) performance status of 2. Moreton *et al.* [11] evaluated alemtuzumab monotherapy administered to maximal response in patients relapsed or refractory to fludarabine and reported that patients were significantly less likely to respond if their lymph nodes were larger than 5 cm ($p < 0.0001$), if they had received 3 or more previous lines of therapy ($p = 0.0005$), or if their pretreatment WHO performance status was greater than 1.

The RCT published by the German CLL Study Group [20] failed to find a correlation between response status and age, disease stage, response to previous-line fludarabine-containing chemotherapy, cumulative alemtuzumab dose, duration of alemtuzumab therapy, IgH mutational status, or cytogenetic aberrations. However, their analysis was limited to just 11 patients, because the trial was stopped early because of excessive severe infections in the alemtuzumab-consolidation arm.

5. DISCUSSION

In its deliberations, the Hematology DSG places particular emphasis on

- results from published RCTs (where available);
- recognition of a hierarchy of outcomes that should influence treatment decisions, with priority given to therapies found to extend life or improve quality of life; and
- the potential toxicities associated with treatment, with particular emphasis on the toxicities seen in the patients most likely to make up the population eventually to be treated.

The members of the Hematology DSG had considerable difficulty reaching consensus on the appropriate wording of the recommendation for a potential indication for alemtuzumab in patients with CLL. The recommendation went through multiple iterations (see Section 6.4). Based on their review of the available evidence, the DSG considered several interpretations for the use of alemtuzumab in patients with CLL.

The DSG regards alemtuzumab to be an active agent for the treatment of patients with relapsed or