bjh research paper

Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis

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Summary

Hairy cell leukaemia (HCL) was first described 50 years ago. Median survival was then 4 years. The purine analogues, introduced in the 1980s, transformed this prognosis. We reviewed data retrospectively from 233 patients, treated with pentostatin ($n = 188$) or cladribine ($n = 45$), to investigate the current long-term outlook. Median follow-up was 16 years. There were no significant differences in outcome between the two agents. Overall, the complete response (CR) rate was 80% and median relapse-free survival was 16 years. After relapse ($n = 79$) or non-response ($n = 5$), 26 patients received pentostatin and 58 cladribine; 69% achieved CR and median relapse-free survival was 11 years. After third-line therapy ($n = 23$), 50% achieved CR and median relapse-free survival was 6·5 years. However, CRs were equally durable, whether after first, second or third-line therapy. Complete responders and those with both haemoglobin >100 g/l and platelet count $>100 \times 10^9$/l before treatment had the longest relapse-free survival ($P < 0{\cdot}0001$). Patients still in CR at 5 years had only a 25% risk of relapse by 15 years. Outcomes for patients with recurrent disease improved with the monoclonal antibody rituximab, combined with either purine analogue. Overall only eight patients died of HCL-related causes. Patients achieving a CR can expect a normal lifespan.

Keywords: hairy cell leukaemia, pentostatin, cladribine, rituximab, survival.

Hairy-cell leukaemia (HCL) was first described in 1958 (Bouroncle *et al*, 1958) and is recognised as a distinct entity in the World Health Organization (WHO) classification of haematopoietic tumours (Foucar *et al*, 2008). It is a rare and indolent lymphoproliferative disorder, accounting for around 2% of all lymphoid leukaemias (Foucar *et al*, 2008). It is characterised by infiltration of the bone marrow, liver, spleen, and occasionally lymph nodes, by a malignant B-cell with hair-like cytoplasmic projections (Catovsky, 1977). Prior to the introduction of the purine analogues, pentostatin (Nipent; Supergen, Dublin, CA, USA) (Spiers *et al*, 1984) and cladribine (Leustatin; Ortho-Biotech, Bridgewater, NJ, USA) (Piro *et al*, 1990), median survival was only 4 years (Golomb *et al*, 1978). However, treatment with these agents has transformed the course of this disease. A number of retrospective studies have reported overall responses in more than 85% of patients with median relapse-free survival up to 15 years (Piro *et al*, 1990; Cheson *et al*, 1998; Flinn *et al*, 2000; Rafel *et al*, 2000; Goodman *et al*, 2003; Maloisel *et al*, 2003; Jehn *et al*, 2004; Chadha *et al*, 2005; Else *et al*, 2005; reviewed by Lauria & Forconi, 2004).

In a previous report (Else *et al*, 2005) we compared the safety and efficacy of pentostatin and cladribine at a median follow-up of 12·5 years. No differences in outcome were found. Results were similar to those reported in other published series. Survival at 10 years was 96% (pentostatin) and 100% (cladribine) with non-HCL-related deaths censored. We subsequently reported preliminary results in eight patients with recurrent disease who were given the combination of either pentostatin or cladribine with rituximab (Mabthera; Hoffman-La-Roche, Basel, Switzerland) (Else *et al*, 2007), demonstrating improved response rates and relapse-free survival compared with the outcomes in patients re-treated with single-agent pentostatin or cladribine.

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In 2008, the 50th anniversary year of Bouroncle's first description of HCL, and with longer follow-up, we re-analysed the results from this large retrospective series. The primary purpose was to investigate the long-term outcome for patients with HCL treated with purine analogues. The three secondary objectives were: to compare the long-term efficacy of pentostatin and cladribine (in the absence of any randomised controlled trials); to identify factors associated with lack of response, or relapse; and to evaluate the outcome of treatment given to patients with recurrent disease.

Patients and methods

Patients

The Royal Marsden Hospital/Institute of Cancer Research clinical database of 241 patients with HCL was reviewed retrospectively. Six patients remained untreated and two were given combination treatment; the remaining 233 patients, treated between 1986 and 2008 with either pentostatin ($n = 188$) or cladribine ($n = 45$) as a single agent, were included in this study. The series included patients referred to the Royal Marsden from throughout the UK and from 10 other European countries, as well as from Turkey, Israel, Jordan, Iran, Venezuela, Argentina and Australia. There was some crossover of patients at second and third-line treatment (Table I). The median follow-up was 16·0 years (range 1–38 years) from diagnosis.

Diagnosis

The diagnosis of HCL was established in accordance with the WHO criteria (Foucar *et al*, 2008) by morphological, flow cytometric and immunohistochemical analysis of peripheral blood, bone marrow and/or spleen specimens. HCL-variant was excluded by central pathology review.

Treatment

The first 40 patients treated with pentostatin received 4 mg/m^2 intravenously (IV) weekly for the first 4 weeks and every 2 weeks thereafter until maximum response, followed by one additional injection. All other patients received pentostatin 4 mg/m^2 IV every 2 weeks until maximal response, consolidated with two further doses. Cladribine was given by continuous IV infusion at a dose of 0·1 mg/kg/day over 7 d. A repeated cycle of cladribine was given, without interim relapse, in cases where CR was not attained after the first cycle. Such sequential treatment was considered as a single course of treatment for the purposes of this analysis. Prophylactic cotrimoxazole, or nebulised pentamidine, and aciclovir were given to all patients.

Table I. Summary of number of HCL patients receiving treatment at each line of purine analogue therapy.

Line of therapy	Pentostatin	Cladribine	Either plus rituximab	Total
First-line	188	45	–	233
Second-line	26 (22)	58 (9)	5 (3)	89 (34)
Third-line	4 (4)	19 (13)	5 (2)	28 (19)
Fourth/sixth-line	–	–	2 (1)*	–

Numbers in brackets indicate patients re-treated with the same purine analogue.
*Fourth line: $n = 1$; sixth line: $n = 1$.

Most patients who did not respond to initial therapy received second-line treatment with the alternative purine analogue. At recurrence, the majority of patients were re-treated with either the same or the alternative drug (Table I). From 2003, the combination of the monoclonal antibody rituximab with pentostatin or cladribine was given to selected patients with recurrent disease. Rituximab was given IV at 375 mg/m^2, concurrently with pentostatin every 2 weeks in seven patients, or in one patient sequentially, beginning 1 month after completion of pentostatin treatment. With cladribine, rituximab was given weekly from the start of treatment in two patients, or from 2 months after the end of cladribine treatment in two patients.

Evaluation of outcomes

Response was evaluated on completion of pentostatin treatment and at 3–4 months after completion of cladribine therapy, by morphology and immunophenotyping of peripheral blood and bone marrow trephine biopsy. The criteria for response were those of the Consensus Resolution (Anonymous, 1987). Briefly, a complete response (CR) required morphological absence of hairy cells in the blood and bone marrow and normalization of any organomegaly and cytopenias. A partial response (PR) required normalization of peripheral counts, together with at least 50% reduction in organomegaly and bone marrow hairy cells, and <5% circulating hairy cells. All other responses were considered as non-responses (NR). Since 2000, immunostaining with CD20 and DBA44 has been included in the pathological evaluation. The absence of negative staining or of isolated positive cells with either antibody was consistent with CR. Clusters of three or more positive cells indicated residual HCL and were recorded as PR. Relapse was defined as any deterioration in blood counts, confirmed by a bone marrow biopsy showing increased numbers of hairy cells.

Kaplan–Meier curves were calculated for relapse-free survival, progression-free survival and overall survival. Relapse-free survival was measured from the start of purine-analogue treatment until relapse. Progression-free survival was measured from the start of treatment until relapse or death from any cause. Overall survival was measured from the start of treatment until either (a) death from any cause, or (b) death from HCL-related causes with all other deaths censored. Cases

remaining event-free were censored at the date of the latest follow-up.

Statistical analysis

The following statistical tests were used: Chi-square, or Fischer's exact for counts <10 (categorical data), Student's *t*-test (continuous normally distributed data), Mann–Whitney *U*-test (continuous non-parametric data). Kaplan–Meier survival curves were compared using Gehan's Wilcoxon test. Multiple linear regression and Cox regression were used for analysis of variables associated with response and survival respectively. Values of $P \leq 0{\cdot}05$ were considered significant. Analysis was performed using the *Statistica* software package (StatSoft, Tulsa, OK, USA).

This study was approved by the Royal Marsden/Institute of Cancer Research Committee for Clinical Research.

Results

Patient demographics

Median age at diagnosis was 49 (range 23–76) years. Patient demographics at the start of treatment were similar for both treatment groups (Table II), apart from a male:female ratio of 4:1 (pentostatin) vs. 2:1 (cladribine) ($P = 0{\cdot}053$) and a higher median platelet count in the pentostatin group ($P = 0{\cdot}04$). The proportion of patients with haemoglobin <100 g/l and/or platelet count $<100 \times 10^9$/l was not significantly different between the groups (Table II). Absolute neutrophil count at baseline was not available for retrospective assessment. The median follow-up was longer after pentostatin than after cladribine treatment (14 vs. 9 years, $P = 0{\cdot}0002$).

Outcomes

The overall response rate was 97% (96% with pentostatin and 100% with cladribine). The CR rate was 80%: 152 patients (82%) achieved a CR with pentostatin and 34 (76%) with cladribine. These differences were not significant. The median number of pentostatin injections required to achieve a CR was 10 (range 2–27). The median relapse-free survival was 9 years in patients requiring >12 injections ($n = 31$), vs. 16 years in those receiving 12 or fewer ($n = 157$), though this difference was not statistically significant. In eight patients treated with cladribine who still remained in PR, a repeat cycle was given after 4–7 months, without interim relapse, which led to a CR in six patients (75%). Thus 28 patients required one and six required two cycles to achieve a CR. Relapse-free survival was the same whether or not a repeated cycle was required. In univariate analysis, no patient demographic or disease characteristic was associated with the achievement of CR.

Forty-four percent of patients treated with pentostatin and 38% of those who received cladribine relapsed. Relapse rates at 5, 10 and 15 years were 24%, 42% and 47% (pentostatin) and 34%, 42% and 48% (cladribine), respectively (not significant). Overall, patients who were still in CR after 5 years had only a 25% risk of recurrence by 15 years. The median progression-free survival was 10·5 years overall and not significantly different between the two agents. The median relapse-free survival was 16 years overall: 20+ years (not reached) for patients attaining a CR and 5 years after a PR ($P < 0{\cdot}0001$). The results of first-line treatment are summarised in Table III.

Table II. Demographics of HCL patients at first-line therapy.

	First-line treatment		
	Pentostatin $n = 188$*	Cladribine $n = 45$*	Total $n = 233$*
Median follow-up in years since treatment (range)	14 (0·5–22)	9 (0·4–16)	13 (0·4–22)
Median interval in years from diagnosis to purine analogue treatment (range)	1·7 (0–17)	0·5 (0–29)	1·4 (0–29)
Median age in years (range)	52 (24–86)	51 (25–70)	52 (24–86)
Number of males (%)	153 (81%)	31 (69%)	184 (79%)
Number (%) of patients who had prior splenectomy and/or interferon†	108 (59%)	18 (44%)	126 (57%)
Number (%) of patients with splenomegaly (including splenectomized patients)	118 (63%)	28 (67%)	146 (64%)
Median white blood cell count $\times 10^9$/l (range)	3·7 (0–90)	3·0 (0·6–21)	3·5 (0–90)
Median haemoglobin concentration g/l (range)	120 (40–160)	127 (80–160)	120 (40–160)
Median platelet count $\times 10^9$/l (range)	120 (5–695)	75 (22–368)	102 (5–695)
Number (%) of patients with haemoglobin <100 g/l and/or platelet count $<100 \times 10^9$/l	90 (50%)	26 (65%)	116 (52%)

*Minimum number of assessable cases for any variable: 221 (181 pentostatin, 40 cladribine).
†Excluding interferon given for 2–3 months preparatory to purine analogue treatment.

Table III. Response, progression-free and relapse-free survival and relapse rates after therapy.

	Single agent pentostatin or cladribine			Combined with rituximab (2nd, 3rd, 4th or 6th line) $n = 12$
	First line $n = 233$	Second line $n = 84$	Third line $n = 23$	
Overall response rate	97%	97%	100%	100%
Complete response rate	80%	69%	50%	92%
Proportion of responses equivalent or superior to previous line of therapy	N/A	82%	87·5%	100%
Median progression-free survival in years*	10·5	9	6·5	5+ (not reached)
Median relapse-free survival in years*	16	11	6·5	5+ (not reached)

*Includes non-responders.

Compared with all others, the 99 patients (42%) whose disease progressed (who did not respond to treatment, relapsed, or died of HCL-related causes) were no different in gender, age, prior therapy, white blood cell count, spleen size or time from diagnosis until treatment. They were, however, more likely to have haemoglobin <100 g/l ($P = 0{\cdot}008$) and platelet count $<100 \times 10^9$/l at the start of treatment ($P = 0{\cdot}004$). Combining these two variables, the median relapse-free survival of patients with low haemoglobin (<100 g/l) and/or low platelet count ($<100 \times 10^9$/l) was 9 years vs. 20+ years (not reached) for all others ($P < 0{\cdot}0001$). In multivariate analysis, response to treatment was the variable that had the most significant association with relapse-free survival, followed by haemoglobin/platelet count. Within each response group (CR and PR) relapse-free survival was significantly longer for patients who had both higher haemoglobin (≥100 g/l) and higher platelet counts ($\geq 100 \times 10^9$/l) (Fig 1).

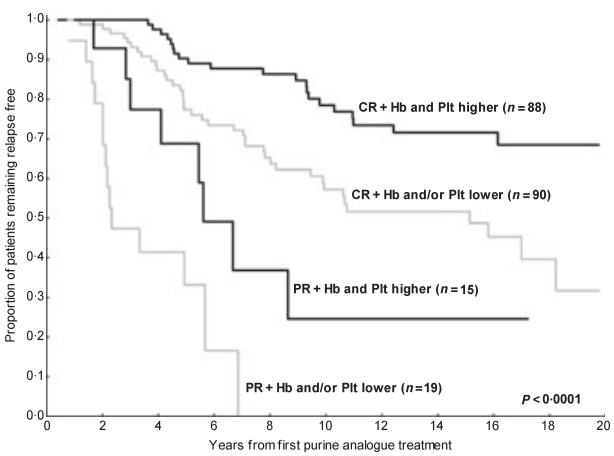

Fig 1. Relapse-free survival after first purine analogue therapy, analysed by blood counts at start of treatment and response to treatment. Relapse-free survival was longest in complete responders with haemoglobin >100 g/l and platelet count $>100 \times 10^9$/l (CR + Hb and Plt higher) and shortest in partial responders with haemoglobin <100 g/l and/or platelet count $<100 \times 10^9$/l (PR + Hb and/or Plt lower).

Outcome of second and third-line treatment

After relapse ($n = 79$) or lack of response ($n = 5$), 26 patients received single-agent pentostatin and 58 cladribine. There were no differences in patient demographics between the two groups, but only four patients (15%) receiving pentostatin had originally received cladribine, whereas 49 (84%) of those receiving cladribine had been treated originally with pentostatin ($P = 0{\cdot}01$, Table I). The overall second-line response rate was 97% (92% with pentostatin and 100% with cladribine) and the CR rate was 69%: 13/24 assessable patients (54%) achieved a CR with pentostatin and 39/51 (76%) with cladribine ($P = 0{\cdot}06$). A shorter median duration of first remission was the only variable associated with failure to attain a CR at second-line therapy ($P = 0{\cdot}03$). A second-line CR (*versus* PR/NR) was the only factor significantly associated with longer second relapse-free survival ($P < 0{\cdot}0001$). Blood counts before the start of second-line treatment were not always available for analysis.

Twelve patients (46%) subsequently relapsed after pentostatin and 19 (33%) after cladribine. Ten years after second-line treatment the rate of relapse was 52% and 40% for the two agents, respectively. Overall, median second-line progression-free survival was 9 years and median relapse-free survival was 11 years, with no significant differences between agents. CR rates, relapse rates, progression-free survival and relapse-free survival were no different between those who changed treatment ($n = 53$) and those re-treated with the same agent ($n = 31$). A summary of results for second-line treatment is shown in Table III.

At third-line treatment (after non-response and/or relapse had occurred twice) four patients received single-agent pentostatin and 19 cladribine. Six changed treatment, while five had the same treatment for the third time. All three evaluable patients treated with pentostatin attained a CR, as did 5/13

evaluable patients treated with cladribine. Summary results for third-line treatment are shown in Table III. The CR rate declined after successive lines of single agent treatment ($P = 0{\cdot}007$, Table III). However, the shorter progression-free survival and relapse-free survival rates after second and third-line treatment were not significant and were only seen in partial responders, while CRs were equally durable, whether obtained with first, second or third-line therapy (Fig 2). None of the eight patients who attained a CR with third-line treatment has yet relapsed after a median follow-up of 4·5 (range 2–11) years.

Outcome of purine analogue and rituximab combination treatment

Twelve patients with recurrent disease were re-treated at second or subsequent lines of therapy (Table I) with either purine analogue plus 3–8 (median 6·5) doses of rituximab, given either concurrently ($n = 9$) or sequentially ($n = 3$). Each had received up to nine (median 2) prior therapies, including splenectomy and interferon. Most had shown poor responses to previous purine analogues (CR rate: 37%) and/or short relapse-free survival (median 2·5 years). At a median follow-up of 2 years (range 0·5–5), the results appeared better than in those retreated with a purine analogue alone (Table III). The only partial responder relapsed after 10 months and subsequently died of HCL. The other 11 patients attained a CR, with no evidence of minimal residual disease assessed by immunohistochemistry, and all currently remain in remission.

Overall survival and second malignancies

There were 45 deaths in this series (19%), equivalent to the rate for the general population when matched by age and sex (UK Statistics Authority, 2008a) (expected $n = 57$, not significant). Overall survival 15 years after first treatment was 78%, or 96% when non-HCL-related deaths were censored (95% pentostatin and 100% cladribine; not significant). Only eight deaths (3·4%) were HCL-related, following refractory disease, of which all but one occurred before 1998. Thirty-one patients developed second malignancies (28 subsequent to HCL treatment), excluding non-melanoma skin cancers. This was equivalent to the incidence of cancers in the general population, matched by age and sex (UK Statistics Authority, 2008b) (expected $n = 33$). Four of these malignancies were leukaemias/lymphomas and two were myeloproliferative disorders. At the latest follow-up, the median age was 65 (range 35–97) years and 91% of the surviving patients were currently in remission, with 79% in CR.

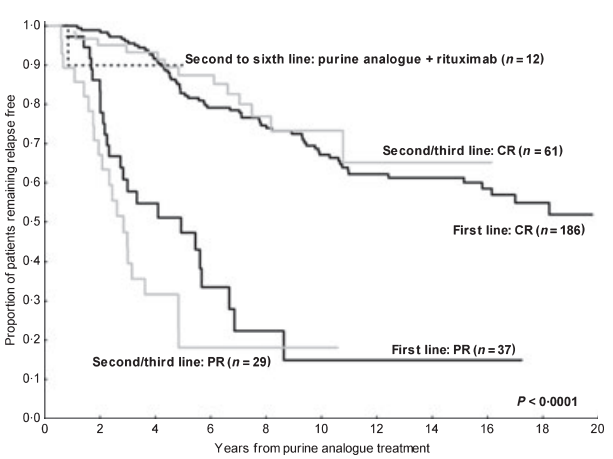

Fig 2. Relapse-free survival analysed by line of therapy and response to treatment. Complete responses were equally durable, whether achieved at first, second or third-line single-agent treatment. The combination of a purine analogue with rituximab in 12 patients with recurrent disease showed encouraging results.

Discussion

The long-term outcome for HCL patients requiring therapy has been transformed in the 50 years since the disease was first identified (Bouroncle *et al*, 1958). At that time, the median overall survival was 4 years, whilst in this series only eight HCL-related deaths have occurred in 233 patients at a median follow-up from diagnosis of 16 years. This change in prognosis is largely due to the introduction of the purine analogues pentostatin and cladribine. Furthermore, seven of the eight deaths occurred before the introduction of rituximab, which has proved beneficial in refractory and relapsed disease when used in combination with a purine analogue (Ravandi *et al*, 2006; Else *et al*, 2007).

This was not a randomised controlled trial and there were minor demographic differences between the two treatment groups. However, there was no evidence that these differences affected the study results. After some cross-over of patients at second-line treatment no demographic differences were apparent.

Outcomes were similar, irrespective of whether patients were first treated with pentostatin or cladribine and irrespective of which treatment was given at second line. In the absence of a randomised controlled trial, these findings suggest the two agents are interchangeable and equal in efficacy.

As in the previous report of this series (Else *et al*, 2005), patients in whom a CR was achieved had longer relapse-free survival than those who only attained a PR (Fig 2) and the CR rate declined with each subsequent line of single agent therapy (Table III). These findings are mirrored in other series (Rafel *et al*, 2000; Goodman *et al*, 2003; Maloisel *et al*, 2003; Jehn *et al*, 2004; Chadha *et al*, 2005) and indicate the importance of persisting with therapy, in the absence of toxicity, until a CR is obtained. A bone marrow biopsy is therefore essential to determine whether this goal has been reached. With longer follow-up, the tendency for relapse-free survival to become shorter after each successive line of therapy was less marked than in our previous report (Else *et al*, 2005) and was only apparent in partial responders. CRs, although progressively less readily attained, lasted equally long, whether at first, second or third-line therapy (Fig 2). However, we cannot exclude the

possibility that the use of immunostaining may have led to the down-grading of responses to second or third-line therapy which would earlier have been considered as CRs. Median relapse-free survival after a CR was at least four times longer than after a PR (Fig 2), once again underlining the importance of achieving a CR at all stages of treatment.

Many different variables have been shown to be associated with poorer outcomes: older age, lower haemoglobin level or platelet count, splenectomy, splenomegaly, lymphadenopathy, leucopenia, leucocytosis, previous treatment, shorter time from diagnosis to treatment and lower performance status (Grever *et al*, 1995; Mercieca *et al*, 1996; Cheson *et al*, 1998; Saven *et al*, 1998; Flinn *et al*, 2000; Rafel *et al*, 2000; Goodman *et al*, 2003; Maloisel *et al*, 2003), reviewed by Dearden and Else (2006). With long-term follow-up, in a disease diagnosed mostly in middle age, deaths from unrelated causes are liable to be an increasingly evident confounding factor for both progression-free survival and overall survival. Hence, relapse-free survival was the endpoint chosen for analysis of prognostic factors in this current study. As in chronic lymphocytic leukaemia, we found that patients with a low haemoglobin and/or platelet count appeared to fare worse (Fig 1).

Early evidence of using rituximab in combination with a purine analogue has shown synergistic action and resulting benefit (Ravandi *et al*, 2006; Else *et al*, 2007; Cervetti *et al*, 2008). Used in the current series, in 12 patients with recurrent disease, the results are encouraging (Table III & Fig 2). The evidence as to whether it should be used concurrently or sequentially is inconclusive (Ravandi *et al*, 2006; Else *et al*, 2007; Cervetti *et al*, 2008) but, based on studies in chronic lymphocytic leukaemia, concurrent treatment may be regarded as preferable, given the synergistic effect of the two agents (Byrd *et al*, 2003). In view of the long remissions obtained after first-line treatment with a purine analogue alone, it may be difficult to justify the extra expense of combination treatment with rituximab for all patients as first-line treatment. However, five categories of patients in our series were less likely than others to attain a CR and/or had shorter relapse-free survival. These patients could therefore benefit from the combination treatment: those with haemoglobin <100 g/l and/or platelet count $<100 \times 10^9$/l at the start of treatment; non-responders to single-agent pentostatin or cladribine; those who had not yet attained a CR after either a single cycle of cladribine or after 12 pentostatin injections; and those who relapsed.

At 16 years median follow-up from diagnosis, one-fifth of patients had died, equivalent to the age/sex-matched death rate for the general population. However, the incidence of HCL-related deaths was less than 4%. The first patients in this series, treated with purine analogues in the mid-1980s, would have had a life expectancy at diagnosis of around 4 years (Golomb *et al*, 1978). Twenty years later, many of these same patients are still disease free. The achievement of a CR is a critical factor in this success and should be the goal of treatment at each stage. Of those who were still in their first CR at 5 years, only one quarter relapsed by 15 years. It is too early to tell whether the much improved results seen in recurrent disease by combining a purine analogue with rituximab will be sustained over time. Currently, the majority of HCL patients can look forward to a normal life expectancy.

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Authorship and conflict of interest statements

Monica Else analysed the data and wrote the paper; all other authors were both treating physicians and editorial advisors. Steve Johnson has acted as a consultant for Johnson & Johnson and Daniel Catovsky for Hospira and Roche. The authors have no further competing financial interests to declare.

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Appendix I

The following investigators participated in this study:

UK: Addenbrooke's Hospital – G Follows, R Marcus; All Saints' Hospital Chatham – JPLA Hayes; Arrowe Park Hospital – TJ Deeble, N Butt; Barnsley Hospital – D Chan-Lam, JP Ng; Basildon Hospital – PLO Cervi, A Pluta; Basildon University Hospital – EJ Watts; Beechcroft Medical Centre – JF Bernstein; Birmingham Heartlands Hospital – DW Milligan; Bristol Royal Infirmary – JA James, GL Scott; Burton Hospital – D Shresvasta; Central Middlesex Hospital – M Brozovic; Chase Farm Hospital – M Treacy; Cheltenham General Hospital – E Blundell, RG Dalton, R Lush; Church Langley Medical Centre – MR Kisenyi; Clementine Churchill Hospital – U Hedge, P Skacel; Colchester General Hospital – MA Boots, M Wood; Colville Health Centre – CA Mok; Dulwich Medical Centre – D Thanga; East Surrey Hospital – P Kaczmarek, F Matthey; Emperor's Gate Centre For Health – HL King; Epsom General Hospital – L Jones, MJ Semple; Farnborough Hospital, Orpington – B Vadher; Fitzalan Medical Centre – W Morgan; Frimley Park Hospital – P Alton, J Shirley J van de Patte; Grove Surgery – SB Kotecha; Harefield Health Centre – AM Hogarth; Havering Hospital – A Brownell; Hillingdon Hospital – D Kaczmarski; Hope Hospital – JB Houghton; Huddersfield Royal Infirmary – J Braithwaite; Ipswich Hospital – I Whalley, NJ Dodd; John Radcliffe Hospital – JS Wainscoat; Kent and Canterbury Hospital – C Pocock; Kidderminster General Hospital – M Lewis; Kingston Hospital – H Sykes; Leicester Royal Infirmary – CS Chapman; Lindfield Medical Centre – AGM Reader; Luton and Dunstable Hospital – DS Thompson; Maidstone Hospital – C Pocock, S Rassam; Manchester Royal Infirmary – JAL Yin; Measham Medical Unit – N Gravestock; Medway Maritime Hospital – JPLA Hayes; Milton Keynes Hospital – E Miller, D Moir; Mount Vernon Hospital – A McMillan; Ninewells Hospital – K Gelly; North Middlesex Hospital – TO Kumaran; Nottingham City Hospital –

A Haynes, NH Russell; Park Road Surgery Camberley – GB Hey; Perth Royal Infirmary – A Heppleston; Poole Hospital – GP Clein; Prestwood House Surgery – D Ghatora, J Redferne; Princess Margaret Hospital – S Green; Princess Royal Hospital – P Hill; Queen Mary's Hospital Roehampton – JA Maitland; Royal Berkshire Hospital – F Booth; Royal Bournemouth Hospital – TJ Hamblin, S Killick, D Oscier; Royal Free Hospital – V Hoffbrand, AB Mehta; Royal Gwent Hospital – EH Moffat; Royal Liverpool University Hospital – A Pettitt; Royal London Hospital – AC Newland; Royal Marsden Hospital – D Catovsky, CE Dearden, E Matutes, N Osuji; Royal Shrewsbury Hospital – NTJ O'Connor; Royal Surrey County Hospital – L Hendry, G Robbins; Royal Sussex County Hospital – JR Duncan; St Bartholomew's Hospital – TA Lister, AZS Rohatiner; St Helier Hospital – J Behrens; St Mary's Hospital Isle of Wight – R Joshi; St Peter's Hospital – ALC Miller; St Richard's Hospital Chichester – CP Bevan, P Stross; St Thomas's Hospital – G Majumdar; Southend Hospital – NE Traub; Stoke Mandeville Hospital – AM O'Hea; Taunton & Somerset Hospital – SAN Johnson; Temple Fortune Health Centre – L Harverd; Treliske Hospital – AR Kruger; Trumpington Street Medical Practice – CM Lea-Cox; University Hospitals Bristol – R Evely; Walton Hospital – D Stevenson, B Woodcock; West Suffolk Hospital – J Koutts; Westbury Avenue Surgery – ATM Hoque; Western General Hospital Edinburgh – D Allen, J Davies; Weybridge Hospital – C Anson; Whipps Cross Hospital – C de Silva; William Harvey Hospital – A Liyanage, V Ratnayake; Worthing Hospital – A O'Driscoll; Wycombe Hospital – S Kelly; *Argentina:* Consultorios de Estudios Hematologicos – LM Barazzutti; *Australia:* Royal Brisbane Hospital – SM Basu; *Belgium:* AZ Sint-Jan van het OCMW – A Van Hoof, A Louwagie; *France:* Assistance Hopitaux Publique de Paris – C Belanger; Groupe Hospitalier Pitié Salpetrière – P Cacoub; *Greece:* Democritus University of Thrace – C Tsatalas; Laikon General Hospital – G Pangalis; Serres General Hospital – M Protopapa; *Iran:* Ahvaz – J Natighi; Shiraz Medical Center – MJ Saalabian; *Ireland:* St Vincent's Hospital – D McCarthy; *Israel:* Beilinson Medical Center – M Shaklai; Chaim Sheba Medical Centre – I Ben-Bassat, A Kneller; Hadassah University Hospital – A Polliack; *Italy:* AOUS, Siena – F Forconi, F Lauria; Ospedale S Gennaro – F Gonnella; *Jordan:* Al-Khalid Hospital – A Abbadi; *Macedonia:* Medical Faculty Skopje – R Stojanovic; *Malta:* St Luke's Hospital – DP Busuttil; *Russia:* Blokhin Cancer Research Center – MA Volkova; National Research Centre for Haematology – L Al-Radi, E Iakhnina; *Serbia:* Clinical Center of Serbia – GM Jankovic, D Tomin; *Spain:* Clinica Puerta de Hierro – R Cabrera Marin; Hospital Clinic de Barcelona – E Montserrat; Hospital General Universitari de Valencia – F Carbonell; Hospital Ntra Sra de la Candelaria – J Garcia-Talavera; Hospital Universitario Marques de Valdecilla – E Conde; Hospital Vall d'Hebron – T Vallespí; *Turkey:* Istanbul Faculty of Medicine – G Dincol; *Venezuela:* Hospital Militar ''Carlos Arvelo'' – MA Paz Castillo.

