Primary care management of early stage chronic lymphocytic leukaemia is safe and effective

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Summary

Background: Chronic lymphocytic leukaemia (CLL) is the commonest leukaemia in western society. Most patients are detected incidentally at an early stage and require ‘watch and wait’ follow-up. In the UK, management of Stage A0 CLL varies with some centres advising regular outpatient haematology follow-up, whereas others recommend management within primary care. The safety and effectiveness of these two management options are currently unknown.

Methods: An observational retrospective cohort study in outpatient Haematology clinics at Queen Elizabeth Hospital Birmingham (QEH) and Birmingham Heartlands Hospital (BHH) and primary care practices in West Midlands, UK. All patients diagnosed with stable stage A0 CLL since 2002 at BHH or QEH were identified. At QEH, patients were discharged to primary care follow-up, whilst QEH patients remained under haematology for follow-up. Evidence of disease progression, need for treatment and overall mortality was documented.

Results: Two hundred and forty-six Stage A0 CLL patients were identified. One hundred and five (43%) patients were discharged to primary care, whilst 141 (57%) patients were followed up in haematology outpatient clinics. No difference in mortality or need for treatment was found between the two groups. Of those discharged, 93 (66%) remained in primary care.

Conclusion: The management of stable-stage A0 CLL within primary or secondary care leads to equivalent clinical outcomes. The prevalence of early-stage CLL is expected to increase with the ageing population and management within primary care should be considered as a potentially effective approach.

Introduction

Chronic lymphocytic leukaemia (CLL) is the most common type of adult leukaemia in the western world, accounting for 35% of all leukaemias.1 Over 4000 new cases are identified per year in the UK, with a median patient age of 71 years.2 The majority of patients are diagnosed incidentally following detection of lymphocytosis after a full blood count (FBC) taken for an unrelated reason.3 With the increasing longevity of the population and widespread use of blood screening tests, the incidence of CLL and its impact on healthcare services is set to increase.4

Stage A0 is used to define CLL patients who have a lymphocyte count of >5 ×10⁹/l without any
symptoms or clinical signs such as lymphadenopathy.\textsuperscript{5,6} A ‘watch and wait’ policy, based on withholding chemotherapy until symptoms arise, is adopted for >70% of patients diagnosed with CLL and the majority of these patients may never require treatment during their lifetime.\textsuperscript{7–9} The management of stage A0 CLL varies within different centres across the UK, with some centres advising regular follow-up in the haematology outpatient setting whereas others recommend management within primary care. The safety, effectiveness, patient satisfaction and cost-effectiveness of these two management options are currently unknown and current practice is divided with half (53\%, \( n = 21 \)) of surveyed UK haematologists with an interest in CLL reporting their local practice to be hospital led follow-up, whilst the other 47\% discharged their patients to primary care (Parry HM. unpublished work).

It has been suggested that follow-up of patients with stage A0 CLL should occur within primary care as most patients will remain stable over time and only require periodic monitoring of their condition.\textsuperscript{7} In the West Midlands, management of patients with stage A0 CLL differs across two large NHS Trusts. Since 2002, Birmingham Heart of England NHS Foundation Trust (BHH) has discharged stage A0 patients who have demonstrated a stable white cell count at their second outpatient appointment, to primary care for ongoing management. In contrast, at the Queen Elizabeth Hospital (QEH), stage A0 patients are seen indefinitely at haematology outpatient clinics at intervals of 6–12 months.

If primary care management was shown to be safe and effective, it has the potential to reduce patient visits to hospital and yield significant cost savings to the NHS. This study aimed to identify current practice in the management of stage A0 CLL in the UK and to compare the safety and clinical effectiveness of primary vs. secondary care management strategies.

**Methods**

**Study design, settings and participants**

This retrospective cohort study compared management strategies and outcomes for patients diagnosed with stage A0 CLL at the Queen Elizabeth and Birmingham Heartlands Hospitals (BHH) between 2002 and 2014. Patients were identified from multidisciplinary team records, and eligible patients were those that had a documented stable lymphocyte count and the absence of symptoms or palpable lymphadenopathy at the first and second outpatient clinic visit as assessed by a consultant haematologist.

The criterion for patient discharge from haematology to primary care follow-up was that a patient remained stage A0 and had exhibited a stable white cell count at their second outpatient haematology appointment. When a patient is discharged to primary care follow-up, patients and their general practitioners (GPs) are given written information advising an annual review and FBC analysis together with criteria for re-referral should there be evidence of disease progression. Criteria for re-referral from primary care back to secondary care management are a doubling of lymphocyte count within 12 months; development of bulky lymphadenopathy, splenomegaly, B symptoms or cytopenias.

For each eligible patient the management decision to discharge to primary care or retain in secondary care was obtained from the patient record. For those discharged to primary care follow-up, the need for subsequent re-referral to secondary care was noted from clinical letters. In addition, adherence to information given by the GP was assessed by the presence of an annual FBC result on the hospital laboratory system. If no record was found, the clinical status of the patient was discussed with the individual GP practice and confirmation of the availability of FBC results was sought.

The outcomes for all eligible patients were obtained from the patient record at the most recent date of contact. Disease progression was identified by the presence of lymphadenopathy, hepatosplenomegaly, cytopenias, serious infection or presence of constitutional symptoms such as fever, night sweats, tiredness and weight loss. The annual lymphocyte doubling time was assessed in those patients for whom this was available.\textsuperscript{7} The white cell count at diagnosis, sociodemographic factors such as age and gender and mortality data were also obtained.

**Statistical analysis**

Analysis comprised descriptive statistics and proportions. Mann Whitney U-test was used for univariate analysis. Categorical variables were assessed using variable counts, proportions and \( \chi^2 \) comparison. Univariate and multivariate binary logistic regression modelling was used to assess the factors associated with disease progression to the point where treatment was needed, and patient mortality. Kaplan–Meier curves were used to assess time to first treatment and patient survival within the primary care and secondary care follow-up cohorts. All statistical analyses were undertaken using SPSS version 21 (IBM Corp, Armonk, NY).
Results

Comparative cohort study

A total of 246 eligible patients were identified from the records of both the QEH (141 patients) and BHH (105 patients). All patients seen at QEH were retained in secondary care for follow-up, whilst all the patients at BHH were discharged to primary care, in line with hospital policy.

Figure 1 shows the flow of patients through the study. Of the 141 individuals who were initially discharged to primary care follow-up, 93 patients (66.0%) remained in primary care follow-up at the point of analysis. Of those patients who were re-referred to secondary care, 77% of re-referrals were assessed to be in accordance with guidelines given to patients and GPs at the point of discharge. Concordance with advice given at discharge was monitored through the presence of an FBC result on the patient record, and a documented result for every year since the point of discharge was located in 79% of cases. Those without a documented FBC were not found to have any adverse outcome during a follow-up telephone conversation with the primary care practice.

There was no statistical difference in the length of follow-up (i.e. the time between diagnosis and last known contact) between primary and secondary care patients. The median length of follow-up for primary care patients was 66 months (inter-quartile range (IQR), 49–94 months), compared with a median length of follow-up of 73 months for secondary care patients (IQR, 48–103 months) (Mann–Whitney U comparison of medians: \( P = 0.312 \)).

Table 1 shows the characteristics of individuals discharged to primary care for follow-up compared with those whose management was retained in secondary care. Analysis was based on a consideration of the association between management setting and patient age, gender, white cell count (WCC) at diagnosis, clinical outcome (remained asymptomatic vs. needed treatment) and survival outcome. The only patient or clinical characteristics that were significantly associated with patient discharge to primary care were age at diagnosis, where the primary care discharge cohort was significantly older (median age of 71 compared with 68 in those followed up in haematology clinics; \( P = 0.02 \)) and white cell count at diagnosis, where the primary care discharge cohort had a significantly higher median WCC than those retained in secondary care (13.2 vs. 10.4; \( P = 0.018 \)). Importantly there was no difference in the proportion of patients in either group that eventually required treatment for CLL progression or in the proportion of patients in each group who died during the study period.

A binary logistic regression analysis was also undertaken to assess whether there were any significant patient (age, gender) or clinical factors (white cell count at diagnosis, management setting) associated with the need for patient treatment or patient mortality between the primary and secondary care follow-up cohorts.
None of the demographic or clinical characteristics (including management setting) were significant predictors of whether or not a patient eventually needed treatment for their CLL, in either univariate or multivariate (adjusted) models. Statistically significant predictors of mortality in both univariate and multivariate analyses were increased age at diagnosis (multivariate OR: 1.09, 95% CI: 1.05–1.12; \( P = 0.0001 \)) and higher white cell count at diagnosis (multivariate OR: 1.02, 95% CI: 1.00–1.04; \( P = 0.04 \)). Importantly, management setting was not a statistically significant predictor of patient mortality in either the univariate or multivariate analyses, suggesting that primary care management is no less effective in terms of treatment or mortality outcomes than secondary care management. Figure 2 shows Kaplan–Meier curves demonstrating that there was no statistically significant difference in survival (\( P = 0.335 \)) or time to first treatment (\( P = 0.188 \)) between those that were discharged to primary care and those who were followed up in a hospital setting.

### Discussion

Currently over 4000 patients are diagnosed with CLL each year in the UK, the majority being aged over 60 years and with early-stage disease.\(^2\) It is agreed that all stage A0 patients should be seen at diagnosis by an experienced haematologist with an in-depth discussion addressing the diagnosis and prognosis.\(^9\) Further management, in particular, for those undergoing surveillance for early-stage disease varies throughout UK between primary and secondary care with no research to date comparing these two forms of follow-up. It is accepted that although many patients will remain stable, an efficient and effective means of follow-up is needed for patients with early-stage CLL, so that any disease progression can be identified promptly and appropriate treatment can be instigated.

This study is the first to assess current CLL management practice across the UK and to compare outcomes for two patient cohorts followed up in primary or secondary care. The results suggest that it is both safe as well as clinically effective to discharge early-stage CLL patients to primary care for ongoing monitoring as it is to follow up patients in the secondary care setting. Outcomes for patients managed in primary care were no worse than for those managed in secondary care despite primary care patients undergoing follow-up assessments annually rather than six-monthly as in haematology clinics.

The psychological aspects of CLL management also need to be considered. The diagnosis of a ‘leukaemia’ can lead to considerable anxiety for both the patient and family members. Being told you have an incurable cancer that may require future treatment but needs continually monitoring can have a significant burden on psychological well-being, particularly in the weeks leading up to the next clinic appointment.\(^10\) Often patients find

### Table 1 The association between patient/clinical characteristics and CLL management setting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discharged to primary care</th>
<th>Retained in secondary care</th>
<th>Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (%)</td>
<td>141 (57.3)</td>
<td>105 (42.7)</td>
<td></td>
</tr>
<tr>
<td>White cell count at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13.2</td>
<td>10.4</td>
<td>( P = 0.015 )</td>
</tr>
<tr>
<td>Range</td>
<td>2.5–107.0</td>
<td>1.9–162.8</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>8.9–20.4</td>
<td>7.0–19.3</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>71.0</td>
<td>68.0</td>
<td>( P = 0.022 )</td>
</tr>
<tr>
<td>Range</td>
<td>50–96</td>
<td>35–94</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>65–78</td>
<td>61–77</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 (56.7)</td>
<td>65 (61.9)</td>
<td>( \chi^2 = 0.47; \ P = 0.493 )</td>
</tr>
<tr>
<td>Female</td>
<td>61 (43.3)</td>
<td>40 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remained asymptomatic</td>
<td>117 (83.0)</td>
<td>82 (78.1)</td>
<td>( \chi^2 = 0.64; \ P = 0.424 )</td>
</tr>
<tr>
<td>Needed treatment</td>
<td>24 (17.0)</td>
<td>23 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Survival outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>98 (69.5)</td>
<td>72 (68.6)</td>
<td>( \chi^2 = 0.02; \ P = 0.888 )</td>
</tr>
<tr>
<td>Deceased</td>
<td>43 (30.5)</td>
<td>33 (31.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Comparison of medians used the Mann–Whitney U-test; comparison of proportions used the \( \chi^2 \) test. 
hospital appointments more emotionally and physically demanding than review within primary care, particularly the very elderly. Our finding that monitoring within primary care is not associated with impaired clinical outcome has the potential to improve quality of life, whilst reducing haematology outpatient waiting times.

Although the majority of early-stage CLL patients follow an indolent course, some will inevitably show progression of their disease. Despite the existence of several biomarkers of poor prognosis, the heterogeneous nature of the disease still presents challenges for predicting which patients will need further treatment. For primary care follow-up to
be effective, excellent communication between the patient and primary and secondary care practitioners is paramount and requires verbal and written information to be shared between all parties. This includes advice regarding recommended vaccinations for CLL patients and awareness of the increased risk of infection in these patients.15

**Conclusion**

This study shows that annual clinical assessment and FBC carried out within the primary care setting for patients with early-stage CLL is comparable to follow up within a specialist haematology outpatient clinic and that primary care follow-up is safe and clinically effective. Follow-up within primary care has the potential to offer considerable practical and financial improvements for health care.

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**References**


