Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial

K M Ardeshna, P Smith, A Norton, B W Hancock, P J Hoskin, K A MacLennan, R E Marcus, A Jelliffe, G Vaughan Hudson, D C Linch, on behalf of the British National Lymphoma Investigation

Summary

Background Neither chemotherapy with a single-alkylating agent nor aggressive combination chemotherapy cures advanced stage low-grade non-Hodgkin lymphomas, even when combined with radiotherapy. Our aim was to compare administration of immediate chlorambucil treatment with a policy of delaying chlorambucil until clinical progression necessitated its use, in asymptomatic patients with advanced-stage, low-grade non-Hodgkin lymphoma.

Methods 309 patients with asymptomatic, advanced-stage, low-grade non-Hodgkin lymphomas were recruited from 44 UK centres between Feb 1, 1981, and July 31, 1990. 158 patients were randomised to receive immediate systemic therapy with oral chlorambucil 10 mg per day continuously. The remaining 151 were randomised to an initial policy of observation, with systemic therapy delayed until disease progression. In both groups, local radiotherapy to symptomatic nodes was allowed.

Findings Median length of follow-up was 16 years. Overall survival or cause-specific survival did not differ between the two groups (median overall survival for oral chlorambucil 5-9 [range 0-17-8] years and for observation 6-7 [0-5-18-9] years, p=0.84; median cause-specific survival 9 [0-17-8] years and 9-1 [0-67-18-9] years, respectively, p=0.44). In a multivariate analysis, age younger than 60 years, erythrocyte sedimentation rate (ESR) 20 mm/h or less, and stage III disease, conferred significant advantages in both overall survival (p<0.0001, 0.03, and 0.03, respectively) and cause-specific survival (p=0.002, 0.008, and 0.001, respectively). In the observation group, at 10 years’ follow-up, 19 patients were alive and had not received chemotherapy. The actuarial chance of not needing chemotherapy (non-lymphoma deaths censored) at 10 years was 19% (40% if older than 70 years).

Interpretation An initial policy of watchful waiting in patients with asymptomatic, advanced stage low-grade non-Hodgkin lymphoma is appropriate, especially in patients older than age 70 years.

Introduction Most patients with low-grade non-Hodgkin lymphoma present with disseminated disease, although many are asymptomatic at the time of diagnosis. Widely differing initial approaches have been used to treat such patients, but none have resulted in long-term disease-free survival in a large proportion of these patients. Although complete remissions might be achieved, these do not last and are usually followed by a relentless pattern of relapse.

Several investigators have addressed this issue by comparing the outcomes of patients who were either treated immediately with chemotherapy or were carefully followed without initial systemic treatment. The first reports were retrospective analyses and showed no benefit of early treatment over a watchful waiting approach. Later prospective randomised studies showed a similar outcome but were limited by small patients’ numbers and short follow-up. Length of follow-up is of particular importance since patients with these indolent lymphomas have a long median survival time.

We describe the long-term results of a large, multicentre, prospective, randomised trial done by the British National Lymphoma Investigation (BNLI). Our aim was to compare immediate chlorambucil therapy with initial observation and delay of systemic treatment until disease progression, in patients with anatomically advanced low-grade non-Hodgkin lymphoma.

Methods Patients Patients older than 18 years, with stage III or IV clinically non-aggressive low-grade non-Hodgkin lymphoma were eligible for this trial. They were recruited from 44 centres across the UK. Informed consent and approval from the local ethics review board was obtained. Low-grade lymphomas were defined according to the BNLI classification developed by Bennett and colleagues, and included lymphocytic well-differentiated lymphomas (equivalent to small lymphocytic lymphomas in the working formulation), follicular lymphomas (small, mixed, and large cell), and lymphocytic intermediate differentiation lymphomas (equivalent to diffuse small cleaved cell lymphomas in the working formulation). The initial diagnosis was made at the local hospital, but randomisation to this trial was not done until the diagnosis had been confirmed by central BNLI review.

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Clinically non-aggressive disease was defined as the absence of all of: (1) pruritus or B symptoms; (2) rapid generalised disease progression in the preceding 3 months; (3) life-endangering organ involvement; (4) significant bone marrow infiltration resulting in bone marrow depression that warranted immediate chemotherapy (defined as haemoglobin <100 g/L, white cell count <3-0×10⁹/L, or platelet count <100×10⁹/L, having excluded other causes of such cytopenias); (5) localised bone lesions detected on radiography or isotope scan (because of concern over the development of pathological fractures); (6) renal infiltration (even if renal function was well preserved); and (7) macroscopic as opposed to microscopic liver involvement. Macroscopic disease refers to disease visible on scans. Bulk disease alone was not an exclusion criterion.

**Patients and procedures**

At the start of the study in 1981, primary endpoints were defined as overall survival and relapse-free survival; no secondary endpoints or subanalyses were specified. Eligible patients were centrally randomised to either immediate treatment with chlorambucil or to a watch and wait policy. The randomisation was a straightforward two-group randomisation with no stratification. The group to which a patient was allocated was determined centrally by opening a numbered sealed envelope. Chlorambucil treatment was given continuously at a dose of 0·2 mg per kg bodyweight daily (maximum 10 mg per kg bodyweight daily), with dose reductions according to blood count. Treatment was continued until complete remission, a further 3 months of identical consolidation treatment was given. Chlorambucil was discontinued immediately after clinical progression, or no response on re-evaluation at 3 or 6 months.

Patients in the watch and wait group were closely monitored at regular intervals (maximum 3 months), and systemic treatment with the same regimen of chlorambucil was started after development of aggressive disease. Aggressive disease was defined as the development of: (1) B symptoms or generalised pruritus; (2) rapid disease progression over a period of 3 months or less; (3) life-endangering organ involvement; (4) clinically significant bone marrow infiltration, resulting in bone marrow depression sufficient to warrant immediate chemotherapy; and (5) development of localised bone lesions seen by radiographic or bone scan, macroscopic liver involvement, or renal infiltration.

In both the chemotherapy and the watch and wait groups, low-dose radiotherapy (1500–2000 cGy) to localised symptomatic nodes was allowed. Because of the nature of the study, patients and clinicians could not be masked. The choice of second line and subsequent chemotherapy was left to the discretion of the treating clinician.

309 patients with clinically non-aggressive, stage III or IV, low-grade non-Hodgkin lymphoma, were recruited into the study over 10 years, from 1981 to 1990. Figure 1 shows the trial profile. Eight centres recruited more than ten patients. Table 1 shows characteristics of patients. The patients in the two groups of the trial are well balanced except for a slight increase in the number of patients, with an erythrocyte sedimentation rate (ESR) greater than 20 mm/h in the chlorambucil group. Data for the lactate dehydrogenase concentration and patients’ performance status at diagnosis were not obtained, because this was not standard practice at the time this trial started. 158 patients were randomised to receive immediate systemic therapy with oral chlorambucil, the remaining 151 patients were randomised to an initial policy of observation, systemic therapy being delayed until disease progression. The two groups of the trial are well balanced for the variables shown in table 1.

This report is based on follow-up data available at Jan 1, 2002, the median length of follow-up at this time being 16 years. Only three patients have been lost to follow-up. Two of these, one from each group, had follow-up information for over 10 years after randomisation. The other patient, who was in the observation group, was lost after 8 years of follow-up. Only one patient, who was randomised to the observation

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**Table 1: Characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observation (%) n=151</th>
<th>Chlorambucil (%) n=158</th>
<th>χ² (p value)</th>
<th>All (%) n=309</th>
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<tr>
<td>&lt;60</td>
<td>74 (50%)</td>
<td>82 (52%)</td>
<td>157 (50%)</td>
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<tr>
<td>61–70</td>
<td>56 (37%)</td>
<td>45 (28%)</td>
<td>101 (33%)</td>
<td>3-73 (0-16)</td>
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<tr>
<td>&gt;70</td>
<td>20 (13%)</td>
<td>31 (20%)</td>
<td>51 (17%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79 (52%)</td>
<td>76 (48%)</td>
<td>155 (50%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>72 (48%)</td>
<td>82 (52%)</td>
<td>154 (50%)</td>
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<tr>
<td><strong>Stage</strong></td>
<td></td>
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<td></td>
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<tr>
<td>III</td>
<td>70 (46%)</td>
<td>64 (41%)</td>
<td>134 (43%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>81 (54%)</td>
<td>94 (59%)</td>
<td>175 (57%)</td>
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<tr>
<td><strong>Bone marrow involved (stage IV only)</strong></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>70 (86%)</td>
<td>76 (82%)</td>
<td>146 (84%)</td>
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<tr>
<td><strong>Histology</strong></td>
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<tr>
<td>Follicular I</td>
<td>68 (45%)</td>
<td>62 (39%)</td>
<td>130 (42%)</td>
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<tr>
<td>Follicular II</td>
<td>32 (21%)</td>
<td>38 (24%)</td>
<td>70 (23%)</td>
<td></td>
</tr>
<tr>
<td>Follicular III</td>
<td>1 (0-7%)</td>
<td>3 (2%)</td>
<td>4 (1%)</td>
<td></td>
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<tr>
<td>Lymphocytic well differentiated</td>
<td>39 (26%)</td>
<td>39 (25%)</td>
<td>78 (25%)</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic intermediate differentiated</td>
<td>9 (6%)</td>
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<td>22 (7%)</td>
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<tr>
<td>Low grade unclassified</td>
<td>2 (1-3%)</td>
<td>3 (2%)</td>
<td>5 (2%)</td>
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<td><strong>Haemoglobin (g/L)</strong></td>
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<tr>
<td>&lt;120</td>
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<td>10 (8%)</td>
<td>22 (8%)</td>
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<tr>
<td>&gt;120</td>
<td>119 (91%)</td>
<td>124 (93%)</td>
<td>243 (92%)</td>
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<td>24</td>
<td>44</td>
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<td><strong>ESR (mm/h)</strong></td>
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<tr>
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<td>99 (74%)</td>
<td>217 (79%)</td>
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<td>&gt;20</td>
<td>23 (16%)</td>
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<tr>
<td>Unknown</td>
<td>10</td>
<td>24</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
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<td></td>
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<tr>
<td>&lt;400</td>
<td>28 (22%)</td>
<td>40 (30%)</td>
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<tr>
<td>&gt;400</td>
<td>101 (78%)</td>
<td>94 (70%)</td>
<td>195 (74%)</td>
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<tr>
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<td>22</td>
<td>24</td>
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</table>

*Percentages in parentheses refer to patients in whom the result was known.*

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The χ² test with Yates’ correction was used to determine the difference between categorical variables in 2×2 tables, otherwise the χ² test was used alone. Multivariate analysis was done with Cox’s proportional hazards model.

Role of the funding source
This trial was funded by the Lymphoma Research Trust. The funding source had no role in the trial design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the report.

Results
The overall survival was similar for both groups. The actuarial 5-year, 10-year, and 15-year overall survival rates were 57% (95% CI 49–64), 35% (28–43), and 21% (16–29), respectively, for the chlorambucil group, and 58% (50–65), 34% (27–42), and 22% (16–30), respectively, for the observation group. Median overall survival for the chlorambucil group was 5·9 years (range 0–17·8) and for the observation group 6·7 years (0·5–18·9) (p=0·84, χ²=0·04, hazard ratio 1·125 [95% CI 0·835–1·517]) (figure 2). The cause-specific survival was determined, and the difference between categorical variables in 2 tables, otherwise the χ² test was used alone. Multivariate analysis was done with Cox’s proportional hazards model.

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but not overall survival. Histological subtype had no effect on overall survival. In a multivariate analysis (table 3), only stage, age, and ESR significantly affected overall survival (p=0·008, <0·0001, and 0·002, respectively) and cause-specific survival (p=0·03, <0·0001, and 0·03, respectively) and but not overall survival. Histological subtype had no effect on overall survival. In a multivariate analysis (table 3), only stage, age, and ESR significantly affected overall survival (p=0·008, <0·0001, and 0·002, respectively) and cause-specific survival (p=0·03, <0·0001, and 0·003, respectively) and cause-specific survival (p=0·008, 0·002, and 0·01, respectively).

110 patients (73%) in the observation group subsequently received chemotherapy. The median time to first systemic treatment was 2·6 years for the entire observation group. 26 (17%) patients in the observation group died without receiving chemotherapy. Six died of cardiovascular disease, five from infection (four of whom had bronchopneumonia), and ten from solid tumours. One patient was lost to follow-up and died of lymphoma, and another died of meningitis, possibly of lymphomatous origin, although this was not proven. In three patients the precise cause of death was not documented, but lymphoma was recorded as a cause of death on the death certificate. For the subsequent analysis, we therefore assumed that five patients died of lymphoma without receiving chemotherapy. Median time from entry into the study to death for these 26 patients who died without receiving systemic treatment for lymphoma was 4·7 years (range 0·5–7·9), and the median age at the time of death was 73 years (61–85). A further 13 (9%) patients are alive and have not yet had chemotherapy. Two patients in this group were lost to follow-up after 8·0 and 10·2 years of follow-up, respectively. When last seen, both these patients were well with no evidence of active lymphoma.

10 years after randomisation, 19 patients in the observation group were alive and had not had chemotherapy. Their actuarial chance of not dying of lymphoma nor needing chemotherapy (with non-lymphoma deaths censored) was 19% (95% CI 13–27) (figure 3). The histology slides from these 19 patients were re-reviewed. Low-grade lymphoma was confirmed in 18. One case, previously reported as a small-cell follicular lymphoma, was noted on review to be chronic thyroiditis. Of the eight cases originally reported as a

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**Table 3: Multivariate and univariate analyses of overall (A) and cause-specific survival (B)**

<table>
<thead>
<tr>
<th>A</th>
<th>Number included in analysis=225*</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p value</td>
<td>Relative risk (95% CI)</td>
<td>p value</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>&lt;0·0001</td>
<td>2·35 (1·74–3·19)</td>
<td>&lt;0·0001</td>
<td>2·08 (1·52–2·86)</td>
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<tr>
<td></td>
<td>Stage</td>
<td>0·004</td>
<td>1·56 (1·15–2·12)</td>
<td>0·03</td>
<td>1·37 (1·00–1·87)</td>
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<tr>
<td></td>
<td>Haemoglobin</td>
<td>0·003</td>
<td>2·31 (1·0–3·83)</td>
<td>0·21</td>
<td>1·43 (0·8–2·45)</td>
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<tr>
<td></td>
<td>ESR</td>
<td>0·0002</td>
<td>1·99 (1·14–2·81)</td>
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<td>1·41 (0·98–2·04)</td>
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<td>Albumin</td>
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<tr>
<td></td>
<td>Treatment</td>
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<td>1·04 (0·78–1·40)</td>
<td>0·97</td>
<td>1·01 (0·75–1·36)</td>
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<table>
<thead>
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<th>B</th>
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<td>1·87 (1·02–3·44)</td>
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<td>Albumin</td>
<td>0·02</td>
<td>1·61 (1·10–2·35)</td>
<td>0·08</td>
<td>1·43 (0·97–2·11)</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0·34</td>
<td>1·18 (0·84–1·68)</td>
<td>0·28</td>
<td>1·21 (0·85–1·71)</td>
</tr>
</tbody>
</table>

* Patients with data for all variables; † Patients with data for age, stage, and ESR.
folicular lymphoma, six were reviewed as folicular, one as small lymphocytic lymphoma, and one as reactive (thyroiditis). Of the ten cases originally called lymphocytic well-differentiated lymphomas, six were reclassified as small lymphocytic lymphoma, and three as marginal zone lymphoma. In one the type of low-grade lymphoma was not classifiable. Of the 19 cases, one remained unclassifiable.

Of the 13 patients who still are alive without receiving systemic treatment, five have had local radiotherapy and do not have clinically detectable disease. Seven were not given any local radiotherapy and have had spontaneous clinical remissions, although they have not had repeated bone marrow examinations and CT scans over the years of follow-up, so minor residual disease cannot be excluded. These spontaneous remissions have been sustained in four patients. Two have subsequently had clinical disease recurrence, whereas the third has relapsed twice and had two further spontaneous remissions but currently has detectable disease. In total, four patients had disease clinically detectable at their last clinic visit.

Analysis of factors predicting for the need for chemotherapy revealed that such patients were more likely to be younger (p=0.003) and male (p=0.03) (figure 4; A, B). With respect to age, an unplanned examination of various intervals suggests that the main distinction is between patients younger than 70 years and those older than 70 years. The likelihood of not receiving chemotherapy or dying of lymphoma after 10 years of the trial was 40% (95% CI 18–67) in the 20 patients who were older than 70, compared with 16% (10–20) in the 131 younger than 70 years. Although the chances of not receiving chemotherapy at 10 years were higher in patients originally classified as having lymphocytic well-differentiated lymphoma, as opposed to follicular lymphoma (37% [95% CI 23–53] vs 13% [7–23], respectively), the difference was not significant (figure 4, C). All 11 patients with low-grade lymphomas that were not classified as either follicular or lymphocytic well-differentiated, needed treatment. Stage of disease, haemoglobin concentration, ESR, and albumin concentration did not predict for the ultimate need for chemotherapy. 40 patients (26%) in the observation group needed systemic treatment within a year of randomisation. These patients did not differ in their characteristics (age, sex, histology, ESR, albumin concentration, and haemoglobin concentration) from the others in the same group (data not shown).

In the chlorambucil group, 100 patients (63%) had complete remission, 43 (27%) partial remission, and 13 (8%) did not respond to treatment. Of those who achieved complete remission, the median time until death from lymphoma or need for next chemotherapy (disease-free survival) was 6·1 years (range 1–19·8). By comparison, in the observation group, of the 110 patients (disease-free survival) was 7·3 years (range 0·8–19·1). A direct comparison of the response rates and the disease-free survival after chemotherapy between the two groups is not valid, however, because not all patients in the observation group received chemotherapy. A more appropriate analysis is a comparison of the time to initiation of second-line chemotherapy or death from lymphoma. Figure 5 shows that more patients in the observation group did not need a second course of systemic therapy or die from non-Hodgkin lymphoma at any time, indicating a substantial advantage of the observation group at this stage of treatment. The median time from randomisation to initiation of second line chemotherapy was 66 months (6–242) in the observation group and 43 months (0–238) in the immediate chemotherapy group.

Figure 4: Factors predicting need for chemotherapy in the observation group

(A) age χ²=7·31, p=0.03. (B) sex χ²=4·43, p=0.04. (C) histological subtype χ²=2·13, p=0.14.

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Chlorambucil

Observation

Patients at risk

reported by Young and colleagues was significantly lower into the GELF study and the other prospective trial low tumour burden. The median age of patients enrolled 5-year survival rate was 78%, but more stringent selection criteria were chosen to select only those patients with a low tumour burden. The median age of patients enrolled into the GELF study and the other prospective trial reported by Young and colleagues was significantly lower than in this one, with the median age at entry being 52 and 51 years, respectively. This might contribute to the higher 5-year survival rates seen. For the whole cohort, a multivariate analysis indicated that age younger than 60 years and stage III, as opposed to stage IV, disease and ESR 20 mm/h or less, conferred both overall and cause-specific survival advantages that were consistent with previous studies. There was no survival advantage with initial chemotherapy when only the older or stage IV patients were analysed (data not shown). Haemoglobin and albumin were not discriminating in this asymptomatic study population but they are in symptomatic patients as noted by others.

Chlorambucil is believed to be a non-intensive treatment although the continuous administration used in this trial was certainly more myelotoxic. Furthermore, trials comparing chlorambucil with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone), including one by the BNLI, have not shown that combination chemotherapy results in improved survival.

Even when anatomically widespread, low-grade non-Hodgkin lymphomas are generally non-aggressive with resulting long median survival times. This finding is especially true when the patient is asymptomatic at the time of presentation. Proper assessment of the effect of different treatment strategies needs a long follow-up. Importantly, the follow-up should be as complete as possible to avoid potential bias when patients are lost.

This BNLI randomised trial is the largest so far. Median length of follow-up, 16 years, is two and a half times median survival. It is also noteworthy that, in 10 years, only one patient was lost to follow-up and since then only two more have been lost.

Follow-up of patients who were managed initially without chemotherapy showed that the median length of time until chemotherapy was started was 31 months, which is comparable with the range 23–36 months reported previously. About a quarter of those patients ultimately receiving treatment did so within a year, but this result was not predictable with the prognostic factors available. 13 patients are alive and have never received chemotherapy and, when the non-lymphoma deaths were censored, the actuarial chance of not needing chemotherapy at 10 years was 19%. In previous trials, some did not need chemotherapy but the follow-up was short. Most of these patients had spontaneous remissions, although some had had radiotherapy to a single nodal region.

In Symmers' seminal description of follicular lymphomas he described spontaneous remission, which has also been documented in the Stanford series of follicular lymphomas. Long-term stability or spontaneous remission has also been recorded in lymphocytic lymphoma. Nonetheless, we thought it important to review again the histology of the 19 patients who were alive 10 years into the trial without systemic treatment. In 18 cases, the low-grade non-Hodgkin lymphoma was confirmed. In the remaining case, now thought to be thyroiditis, cervical lymphadenopathy and splenomegaly was present at diagnosis, but these had not been biopsied.

The chances of not needing chemotherapy were particularly high in the small group of patients who were older than 70 years (40% after 10 years of the trial). Whether fewer patients older than 70 years needed chemotherapy because of a difference in disease biology or a reluctance of clinicians to start chemotherapy in older patients is difficult to judge. Nonetheless, there can be little justification for immediate chemotherapy in this group of asymptomatic patients. In patients who were younger than 70 years, the chance of not needing chemotherapy was much less (16% after 10 years), making a watch and wait strategy less attractive, though still appropriate, in this younger group of patients.

In both age groups, a watch and wait policy does not result in improved survival despite delaying the start of chemotherapy for about 2.5 years and delaying the time to initiation of second chemotherapy by nearly 2 years.

There is, therefore, still a need for well designed randomised trials of potentially curative immediate treatment in young patients who are asymptomatic. Long follow-up in such trials will be essential. One of the most intensive strategies explored so far has been high-dose treatment and stem-cell transplantation after standard dose therapy, but the survival curves show no evidence of a plateau, suggesting that this approach is not curative. There might be a proportion of patients cured by allogeneic transplantation, but morbidity and mortality are formidable. Even with non-myeloablative allograft protocols procedure-related mortality is 10% or greater and few patients would probably choose this treatment as part of their planned initial management.

A recent pilot study with CHOP plus the CD20 antibody rituximab has shown encouraging results with more than 50% of patients not having progressed during a median follow-up period of 5 years, and this approach merits testing in a large randomised trial. An alternative strategy in asymptomatic patients would be to offer rituximab therapy alone. In a phase II trial, a response rate of 73% was noted with 57% of patients achieving a complete molecular remission in the blood.

Figure 1. Patients not needing second chemotherapy (%)

Figure 2. Time to second chemotherapy in both groups

Hazard ratio 1.422 (95% CI 1.086–1.861) χ²=6.57, p=0.01.

Discussion

In this trial, overall survival and cause-specific survival did not differ between the observation group and the chlorambucil group, which confirms the results of previously reported trials that were smaller and had shorter follow-up than did ours. The 5-year overall survival was 58% in the observation group and 57% in the chlorambucil group, which is very similar to O'Brien and colleagues' results. The overall survival at 5 years is less than that recorded in other studies, and could be an indication of patient selection. In the GELF trial, the 5-year survival rate was 78%, but more stringent selection criteria were chosen to select only those patients with a low tumour burden. The median age of patients enrolled into the GELF study and the other prospective trial reported by Young and colleagues was significantly lower than in this one, with the median age at entry being 52 and 51 years, respectively. This might contribute to the higher 5-year survival rates seen. For the whole cohort, a multivariate analysis indicated that age younger than 60 years and stage III, as opposed to stage IV, disease and ESR 20 mm/h or less, conferred both overall and cause-specific survival advantages that were consistent with previous studies. There was no survival advantage with initial chemotherapy when only the older or stage IV patients were analysed (data not shown). Haemoglobin and albumin were not discriminating in this asymptomatic study population but they are in symptomatic patients as noted by others.

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Figure 5: Time to second chemotherapy in both groups

Hazard ratio 1.422 (95% CI 1.086–1.861) χ²=6.57, p=0.01.
treatment does not have the toxicity of chemotherapy and might further delay the need for chemotherapy. It could even lead to improved survival, although many years of follow-up would be needed to prove this conjecture. For patients of all ages not in trials, the watch and wait policy remains entirely appropriate.

Contributors
K M Ardeshna, P Smith, and D C Linch were mainly responsible for data collection, initial data analysis, and interpretation and writing the initial draft of the manuscript. G Vaughan Hudson and A Jelliffe instigated the trial. K A MacLennan and A Norton were responsible for the central histological review of diagnostic tissue samples. The other authors were responsible for the final data interpretation and producing the final draft of the manuscript, and recruitment of patients into the trial and providing long-term follow-up data.

Conflict of interest statement
None declared. As corresponding author, KMA had full access to the data, and had final responsibility for the decision to submit for publication.

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References
13 Symmers D. Giant follicular lymphadenopathy with or without splenomegaly. Arch Path 1938; 26: 603–47.