Patients’ experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial

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This is an original article. An abstract (no. 2062) and poster were presented at ASH 2007. Otherwise the material in this paper has not been previously presented, nor previously submitted, elsewhere. This study reports one endpoint (HRQoL) of the LRF CLL4 trial, registration no: ISRCTN58585610.

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Running title: HRQoL at baseline in CLL patients requiring therapy
Summary
We examined the effects of active untreated chronic lymphocytic leukaemia (CLL) on health-related quality of life (HRQoL), measured by the EORTC QLQ-C30 questionnaire at randomisation into the LRF CLL4 trial. Patients were scored 0-100 within each of 15 domains. A difference between groups of ≥10 points was deemed clinically significant (asterisked * below). 431 valid baseline questionnaires were returned. Compared with population norms, patients had impaired HRQoL in 13/15 domains. The greatest differences were in fatigue*, sleep disturbance*, role functioning and global HRQoL. Fatigue was reported by 81% of patients, compared to the next most common symptoms: sleep disturbance (56%) and dyspnoea (49%). There was no association between spleen, liver or lymph node enlargement, or lymphocytosis and any HRQoL domain. Older age (≥70 years) was associated with poorer physical functioning (p<0.001) but fewer financial difficulties (p<0.001*). Impairment of HRQoL at baseline was most apparent in stage A-progressive patients with B-symptoms and stage C patients with haemoglobin <12g/dl: compared with all others, these patients had poorer physical, role and social functioning, more fatigue and dyspnoea and poorer global HRQoL (all p≤0.001*). These findings support the recommendation to begin treatment when patients experience symptomatic disease, to improve HRQoL.

Keywords
Health-related quality of life, chronic lymphocytic leukaemia, untreated patients, B-symptoms, anaemia
Introduction

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in the Western world. Symptomatic patients require chemotherapy [Hallek et al, 2008] and no treatment regimen has yet demonstrated a survival benefit. Thus health-related quality of life (HRQoL) is a key endpoint for patients. However, a recent literature review [Molica, 2007] found few published studies of patients’ self-reported HRQoL in CLL, totalling only 1477 patients and including only two randomised controlled trials: the German CLL4 [Eichhorst et al, 2007] and our own LRF CLL4 [Catovsky et al, 2007] trials. Since then Shanafelt et al [2007] have reported an international web-based survey of HRQoL in 1482 CLL patients, at various disease and treatment stages. Other smaller studies have also included both treated and untreated patients [Bertero et al, 1997; Holzner et al, 2001; Holzner et al, 2004; Levin et al, 2007]. There is little information about the impact on HRQoL of active untreated CLL, as distinct from early stage “watch and wait”. We therefore analyzed in detail baseline HRQoL data from the LRF CLL4 trial, in order to understand the effects of the disease itself, before these became indistinguishable from treatment-related effects.

Materials and Methods

The trial

The LRF CLL4 trial was a randomised controlled trial, with 777 previously untreated CLL patients randomised between 1999-2004 to receive either fludarabine (alone or in combination with cyclophosphamide), or chlorambucil [Catovsky et al, 2007]. There were 136 participating centres, mostly in the UK, but also including Argentina, Croatia, Greece, Ireland, Italy, New Zealand and Russia. Indications for treatment were Binet stage A-progressive, B or C disease. Stage A-progressive was defined by at least one of the following: lymphocyte doubling time <12 months; a downward trend in haemoglobin and/or platelets; >50% increase in the size of the liver and/or
spleen and/or lymph nodes, or appearance of these signs if not previously present; constitutional symptoms (“B-symptoms”) attributable to the disease, e.g. pyrexia, night sweats, weight loss. Patients with life-threatening co-morbidity were excluded from the trial. There was no upper age limit. The trial was approved by the UK multicentre research ethics committee (MREC). All patients gave written informed consent.

**HRQoL instrument**

Using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30 version 2.0) [Aaronson *et al.*, 1993] we measured HRQoL at randomisation (reported here) and at 3, 6, 12, 24, 36, 48 and 60 months. This cancer-specific instrument has been extensively validated [Aaronson *et al.*, 1993; Hjermstad *et al.*, 1995; Kaasa *et al.*, 1995; Groenvold *et al.*, 1997], in more than 60 languages [Koller *et al.*, 2007], and used in a large number of clinical trials. The questionnaire was administered to patients in their primary language. No CLL-specific add-on module was available. Missing data were handled according to the EORTC QLQ-C30 Scoring Manual [Fayers *et al.*, 2001]. Patients were scored 0-100 within each of 15 HRQoL domains, including 5 functional scales (physical, role, social, emotional and cognitive functioning), a global HRQoL scale, 3 symptom scales (fatigue, pain and nausea/vomiting) and 6 single items (dyspnoea, appetite loss, sleep disturbance, diarrhoea, constipation and financial difficulties).

A preliminary analysis of HRQoL change from baseline to 2 years was included in the main LRF CLL4 report [Catovsky *et al.*, 2007]. We will report further on assessments up to 5 years when follow-up is available, to determine the effect of treatment allocation on HRQoL and to examine how far treatment can resolve reduced baseline HRQoL.
Statistical analysis

We hypothesised that baseline demographic and disease characteristics would impact on HRQoL. Differences in these characteristics between patients who returned a valid baseline questionnaire and those who did not were assessed using the Pearson chi-square test (for categorical variables, including those listed below, plus also response to treatment, WHO performance status after treatment and vital status at 2 years) and Student’s t-test (for continuous variables, including age, time since diagnosis and blood counts). Mean HRQoL scores were calculated for the following (categorical) variables: age, sex, nationality, time since diagnosis, disease stage, white blood count, percentage lymphocytes, haemoglobin and platelet levels, enlargement of liver, spleen or lymph nodes in neck, axillae or groin, cytogenetic abnormalities p53 and/or 11q deletion and presence (versus absence) of each defining characteristic in stage A-progressive disease. WHO performance status was not assessed until the end of treatment and was therefore not included. Mann-Whitney U (comparing 2 groups) or Kruskall-Wallis (3 or more groups) non-parametric tests of HRQoL were used. Only p-values ≤0.01 were considered significant. Multiple regression was used only in the HRQoL domains whose mode was other than 0 or 100 (and which therefore approached a normal distribution) to conduct bivariate analyses of variables (continuous and categorical) with a p-value in univariate analysis of <0.05. The prognostic value of baseline HRQoL was calculated using multiple regression (for response to treatment) and Cox’s proportional hazard model (for progression-free and overall survival). All analyses were performed using the Statistica software package (StatSoft, Tulsa, Okla).

Clinical significance

Statistical significance partly reflects sample size and therefore HRQoL reports need to include a measure of clinical significance, i.e. a difference noticeable to patients. Patients have described a change of 5-10 points in the EORTC QLQ-C30 as “a little”
change, 10-20 as “moderate”, and more than 20 as “very much” change [Osoba et al, 1998]. A difference of ≥10 points may therefore be regarded as clinically significant [King, 2001].

Reference values

General population reference values (means and standard deviations by age/sex sub-group) for the EORTC QLQ-C30 are available from Norway and Sweden [Michelson et al, 2000; Fossa et al, 2007]. To minimise cultural bias we combined these results, producing reference means and standard deviations matched by age and sex to LRF CLL4 baseline questionnaire respondents. A valid statistical comparison could not be made because the data were skewed and some sub-groups in the LRF CLL4 sample were too small.

Results

Compliance and patient characteristics

Of 777 patients enrolled in the LRF CLL4 trial 603 (78%) completed a baseline EORTC QLQ-C30 questionnaire. The protocol specified that these should be completed at the start of chemotherapy. A sensitivity analysis showed that 157 questionnaires, completed on the day treatment began, were no different from those completed earlier. However 172 late baseline questionnaires, completed one or more days after treatment started, differed significantly from the rest in ways suggesting the influence of treatment-related effects. These 172 questionnaires were therefore excluded. The 431 patients (55%) who responded before the start, or on the first day, of therapy are included in this analysis. Their demographic and disease characteristics (summarised in Table I) did not differ in any respect from those of patients with late or missing questionnaires, other than a slightly lower rate of returns than expected amongst stage A-progressive patients with B-symptoms (p=0.06) . Nor were they different in terms of subsequent outcomes: response to treatment (78% vs
81%, \( p=0.3 \)), WHO performance status ‘0’ at end of treatment (58% vs 65%, \( p=0.09 \)), alive at 2 years (84% vs 84%, \( p=0.9 \)). We therefore conclude that the compliance rate did not introduce significant bias.

Reference values

Figure 1 compares baseline HRQoL scores with age/sex-matched population norms. Trial patients had lower scores than the norm on all functioning scales and global HRQoL. They also experienced more symptoms in every domain except pain and diarrhoea. These differences were small to moderate (1-12 points). Fatigue and sleep disturbance reached clinical significance (10.6 and 11.9 points difference respectively). Otherwise the largest differences were in role and social functioning, appetite loss and global HRQoL (9.9, 9.1, 9.3 and 9.9 points respectively).

Variables associated with baseline HRQoL

All the study variables significantly associated with poorer HRQoL scores are shown in Table II. Women reported more sleep disturbance than men. Older age (\( \geq 70 \) years) was associated with lower physical functioning scores but with fewer financial difficulties (9.4 and 16.9 points difference, respectively, compared to <60 years). In particular, 64/206 patients (31%) below UK state pension age (females <60 and males <65 years) reported financial difficulties compared with only 22/219 patients (10%) over that age (\( p<0.001 \)). Scores for Stage A-progressive were better than for stage C, and worse than stage B, in physical, role and social functioning, global HRQoL, fatigue and dyspnoea (Table III), but not significantly different from either. Stage C patients with anaemia (haemoglobin <10g/dl) had poorer HRQoL than stages A-progressive and B, while those with thrombocytopenia alone (haemoglobin \( \geq 10 \)g/dl) did not (Tables II & III). In stage A-progressive, haemoglobin level (10-11.9 vs \( \geq 12 \) g/dl) was not associated with HRQoL scores in any domain (\( p\geq 0.3 \), maximum difference 6 points, data not shown), but the presence of B-symptoms in stage A-
progressive was associated with impaired HRQoL across several domains (Tables II & III). The median time from diagnosis until treatment was longer for stage A-progressive questionnaire respondents: 19 months versus 8 months (stage B) and 3 months (stage C) (p<0.001). Within stage C it was longer for questionnaire respondents with thrombocytopenia alone (median 9 months) than for those with anaemia (median 1 month) (p=0.007). Nevertheless, time from diagnosis was not associated with any HRQoL domain in these groups.

Fatigue was reported by 81% of patients, compared to the next most common symptoms: sleep disturbance (56%) and dyspnoea (49%). Only lower haemoglobin level (<11 vs ≥11 g/dl) and B-symptoms in stage A-progressive disease were found to be associated with a level of fatigue above the study norm (Table II). There was no association between HRQoL and nationality (UK versus non-UK), time since diagnosis, spleen, liver or lymph node enlargement, lymphocytosis, poor risk cytogenetic abnormalities or any characteristic of stage A-progressive disease besides B-symptoms. No other significant effects were found.

HRQoL showed most impairment in stage A-progressive patients with B-symptoms. Stage B patients with haemoglobin ≥12g/dl showed the least impairment (Table III). There were some small to moderate differences in HRQoL scores between stage B and C patients with the same haemoglobin level and also some small to moderate differences within each of these two stages according to whether haemoglobin level was 10-11.9 or ≥12 g/dl (Table III). However, neither variable reached p≤0.01 when included together in bivariate analyses conducted in the two eligible domains: global HRQoL (mode: 66) and fatigue (mode: 33), irrespective of whether the analyses included all patients, or just stages B and C. Only 3-5% of the variability between groups was accounted for by these two variables (r² range 0.03-0.05) and no other variable reached significance in any pairing. On the other hand, B-symptoms reached
p≤0.01 in all bivariate pairings in stage A-progressive, alone accounting for 9% of the variability between groups in both global HRQoL and fatigue.

We identified a group of patients with one or more mean baseline HRQoL scores ≥10 points below the study mean (stage A-progressive patients with B-symptoms and stage C patients with haemoglobin <12g/dl, n=142, “group 1”) and a group (stage A-progressive with no record of B-symptoms, all stage B, and stage C with haemoglobin ≥12g/dl, n=289, “group 2”) whose mean scores were less impaired (Table III and Figure 2). The greatest differences between these two groups were in physical, role and social functioning, fatigue, dyspnoea and global HRQoL. We investigated whether the former group had worse prognosis. Stage A-progressive patients with B-symptoms had the same overall response to treatment, progression-free survival (PFS) and survival as other stage A patients (data not shown). Although stage C patients with anaemia (haemoglobin <10g/dl) had fewer responses to treatment (p=0.006) and shorter PFS (p≤0.001) and survival (p=0.004) than those categorised as stage C due to thrombocytopenia alone, altogether group 1 showed no differences in clinical outcomes compared to group 2 (data not shown).

No baseline HRQoL domain predicted response to treatment. Physical functioning was the only domain which, at baseline, already showed an association with PFS (p=0.04) and survival (p=0.003).

Discussion

By analyzing in detail the baseline HRQoL questionnaires of as yet untreated CLL patients we were able to study the effect of the disease itself on HRQoL, unaffected by treatment. Others have collected data from untreated patients [Holzner et al, 2004; Eichhorst et al, 2007; Shanafelt et al, 2007; Levin et al, 2007]. In a single-centre study of 43 untreated and 33 treated patients followed over 1 year, using the
EORTC QLQ-C30, Holzner et al [2004] found slightly, but not significantly, better HRQoL and fewer symptoms in the untreated group. Levin et al [2007], in a single-centre study comparing 58 untreated “watch and wait” and 47 treated patients, using a battery of other validated questionnaires, found no differences in the main outcome variables, depression, anxiety and physical/mental QoL. It is probable that the untreated patients in both studies ranged from those with early stage disease to others with stage A-progressive disease involving B-symptoms. The treated patients may have ranged from those in symptom-free remission to others with terminal disease. Mean scores may therefore have masked very different patient experiences.

The web-based survey by Shanafelt et al [2007] obtained responses from 891 untreated and 591 treated self-selected patients from 35 countries, who completed the Functional assessment of cancer therapy-general (FACT-G) measure of HRQoL and the Brief Fatigue Inventory. Previously treated patients were found to have lower physical (p<0.001) and functional (p<0.001) well-being than untreated patients and more fatigue (p<0.001), but higher social/family (p<0.001) and emotional (p=0.003) well-being, with similar overall HRQOL. The high proportion of younger patients (median age 59 years) and the self-selected nature of these respondents may have helped to limit confounding variables in this large sample, making differences between untreated and treated patients apparent. Amongst the complexity of disease states in untreated and treated patients in the published series, our baseline data have the advantage of being standardised at the point when treatment is indicated.

Eichhorst et al [2007], reporting change from baseline in a randomised controlled trial, noted a small HRQoL improvement by two years in patients given the more effective protocol treatment (fludarabine with cyclophosphamide). LRF CLL4 [Catovsky et al, 2007] (our data) confirmed this finding and showed that patients who responded to treatment had a global HRQoL score 9.1 points higher at 3 months.
than that of non-responders (p=0.0001) and 10.5 points higher at 2 years (p=0.0004).

In our current analysis we found that certain groups of patients (stage A-progressive
with no record of B-symptoms, all stage B, and stage C with thrombocytopenia but
haemoglobin ≥12 g/dl, shown as group 2 in Figure 2) had mean baseline scores not
far short of the population norm (Figure 1). Scores in this group (comprising 67% of
our sample) would therefore not be expected to show much improvement after
treatment, possibly explaining why mean changes from baseline are not larger in
these two randomised controlled trials. We will investigate this point with further
follow-up.

Overall, our LRF CLL4 patients had only moderately reduced HRQoL at baseline
compared to the available normative population data. Eichhorst et al [2007],
comparing CLL patients at baseline with population reference data, found the most
marked differences in largely the same domains as in our study: role functioning and
fatigue, followed by social functioning and sleep disturbance. Compared to other
cancers, our mean scores are consistent with those from groups with the least
extensive/severe cancers [King, 1996]. In an international study of 354 pre-treatment
cases of lung cancer, using the EORTC QLQ-C30 questionnaire, scores were more
than 10 points (maximum 18 points) worse than in our CLL patients in the following
domains: physical and role functioning, pain, dyspnoea, appetite loss and
constipation [Aaronson et al, 1993]. In another international cohort of 735 patients
with advanced cancers [Coates et al, 1997], mean scores were ≥10 points lower than
in LRF CLL4 in physical and cognitive functioning and global HRQoL and ≥25 points
lower in role, social and emotional functioning. However, the difference between our
stage A-progressive patients with B-symptoms and the general population was
moderate to large: 13-28 points in 11 of the 15 HRQoL domains. Values for this
group were similar to those of cancer patients with moderately extensive/severe
disease [King, 1996].
In their internet-based CLL sample, Shanafelt et al [2007] found that emotional well-being, alone, was well below the general population norm (p<0.001) and also below other cancers. They hypothesised this might be due to the failure to recognise and address the emotional impact of CLL on early stage patients. Our findings support this observation, in that the greatest impairment in emotional functioning was seen in stage A-progressive patients with B-symptoms and stage C patients with haemoglobin 10-11.9 g/dl (Table III), both groups having a relatively long median “watch and wait” period before start of treatment, as well as impaired HRQoL in several domains, a combination likely to be experienced as emotionally stressful.

The relevance of haemoglobin levels to HRQoL in haematological malignancies has been much discussed [Molica, 2005; Stephens et al, 2005; Wisloff et al, 2005]. In a multivariate analysis of 745 multiple myeloma patients who had completed the EORTC QLQ-C30 at diagnosis, Wisloff et al [2005] found that extent of skeletal disease was related to physical and role functioning, global HRQoL and pain, whereas haemoglobin concentration was independently related to fatigue alone. They found that there seemed to be a reciprocally potentiating effect of both variables on fatigue and concluded that a change in haemoglobin concentration alone, without modification of objective disease parameters, would be expected to have limited impact on HRQoL. We found a similarly complex relationship between disease stage and haemoglobin level, with clinically significant differences seen in several domains both between stages B and C and within these two stages according to haemoglobin level (Table III). Neither variable emerged as independently significant in bivariate analyses, perhaps not surprisingly, given that haemoglobin level is one of the characteristics which define the different disease stages. In stage A-progressive patients the presence of B-symptoms was the most important variable, while haemoglobin level had no effect.
Data were not collected concerning some potentially important variables such as co-morbidity, or incidence and severity of infections. Consequently the study variables accounted for only a small proportion of the variability between HRQoL scores. It is not known whether B-symptoms impacted equally on HRQoL in stages B and C disease, as we did not have data, nor whether the HRQoL impairment seen in stage A-progressive was due to the B-symptoms themselves or to other constitutional features of CLL when B-symptoms are present. The potential influence of biological factors, including cellular and immune characteristics of CLL, is also presently unclear.

In conclusion, we found that active CLL, before treatment, has an adverse impact on HRQoL. In particular, patients of working age were 3 times as likely to have health-related financial difficulties as those old enough to be in receipt of a state pension, a finding which may have implications for state welfare benefits. The greatest HRQoL impairment, equivalent to moderately extensive/severe disease in other cancers, was seen in stage A-progressive patients with B-symptoms, followed by stage C patients with haemoglobin <12g/dl (Table III and Figure 2). The impairment in several areas of functioning, high level of symptoms and poor global HRQoL reported by stage A patients who have B-symptoms may currently be underestimated in clinical practice. Discrepancies between doctors’ perceptions of HRQoL and those of patients are well recognised [Slevin et al, 1988]. Our findings challenge the frequent practice of a continued “watch and wait” policy for these symptomatic patients. We have previously reported that global HRQoL improved, in our series, in patients who responded to treatment [Catovsky et al, 2007]. While we have yet to investigate the effects of treatment on the HRQoL of any specific group of patients, taken together these findings lend weight to the recommendation [Hallek et al, 2008] to begin
treatment for CLL when patients experience symptomatic disease, in order to induce remissions and thereby improve quality of life in the medium term.

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Figure Legends:

Figure 1
Mean EORTC QLQ-C30 health-related quality of life scores at baseline in 431 LRF CLL4 patients compared to an age/sex-matched sample of 3996 patients, compiled from 2 studies of the general population [Michelson et al, 2000; Fossa et al, 2007]. Standard deviations are shown by error bars.

Figure 2
Mean EORTC QLQ-C30 health-related quality of life scores at baseline:
Group 1: stage A-progressive patients with B-symptoms (n=38); stage C patients with haemoglobin <12g/dl (n=104).
Group 2: stage A-progressive patients without (n=68) or with no record (n=5) of B-symptoms; all stage B (n=189); stage C patients with thrombocytopenia but with haemoglobin ≥12g/dl (n=27).
Table 1: Demographic and disease characteristics: baseline EORTC QLQ-C30 questionnaire respondents compared with patients without a valid baseline questionnaire

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Valid baseline HRQoL questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes* (n=431: 55%)</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>64 (43-85)</td>
</tr>
<tr>
<td>No. of males</td>
<td>319 (74%)</td>
</tr>
<tr>
<td>No. of patients from outside the UK</td>
<td>55 (13%)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
</tr>
<tr>
<td>Months since diagnosis: median (range)</td>
<td>8 (0-179)</td>
</tr>
<tr>
<td>No. of patients at Binet stage:</td>
<td></td>
</tr>
<tr>
<td>A progressive</td>
<td>111 (26%)</td>
</tr>
<tr>
<td>B</td>
<td>189 (44%)</td>
</tr>
<tr>
<td>C</td>
<td>131 (30%)</td>
</tr>
<tr>
<td>White blood count x10^9/l: median (range)</td>
<td>99 (5-605)</td>
</tr>
<tr>
<td>Hemoglobin g/dl: median (range)</td>
<td>12.3 (4-17)</td>
</tr>
<tr>
<td>Platelets x10^9/l: median (range)</td>
<td>155 (23-684)</td>
</tr>
<tr>
<td>No. of patients with poor prognosis cytogenetic abnormalities:</td>
<td></td>
</tr>
<tr>
<td>p53 del ≥20% and/or 11q del (≥5%)</td>
<td>86/335 (26%)</td>
</tr>
<tr>
<td>Stage A-progressive only (overlapping categories)</td>
<td></td>
</tr>
<tr>
<td>No. of patients with:</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte doubling time &lt;12 months</td>
<td>61/106 (58%)</td>
</tr>
<tr>
<td>Downward trend in hemoglobin/platelets</td>
<td>43/106 (41%)</td>
</tr>
<tr>
<td>Increase in nodes/spleen</td>
<td>65/108 (60%)</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>38/106 (36%)</td>
</tr>
</tbody>
</table>

HRQoL = health-related quality of life

* No significant differences; p-value range: p=0.8 to p=0.06
Table II: Variables associated with poorer EORTC QLQ-C30 health-related quality of life scores at baseline in the CLL4 trial
(minimum n=425 for any variable or scale, except where otherwise specified)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline HRQoL domain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(worst HRQoL group first)</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
</tr>
<tr>
<td>Gender (F; M)</td>
<td>NS</td>
</tr>
<tr>
<td>Age group (≥70; 60-69; &lt;60 years*)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Binet stage (C; A; B)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (&lt;11; ≥11 g/dl)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets (&lt;100; ≥100 x10^9/l)</td>
<td>NS</td>
</tr>
<tr>
<td>Stage C without anaemia (Hb≥10g/dl **); all stage A/B</td>
<td>NS</td>
</tr>
<tr>
<td>Stage C with anaemia (Hb&lt;10g/dl); all stage A/B</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>B-symptoms in stage A (Y; N) (minimum n=108)***</td>
<td>NS†</td>
</tr>
</tbody>
</table>

HRQoL = health-related quality of life;
NS = not statistically significant (p>0.01);
Hb = haemoglobin;
† clinically significant (1): (difference between groups ≥10 points);
* reverse order for financial difficulties;
** platelets <100 x10^9/l;
*** Y = B-symptoms present; N = no B-symptoms or (n=5) no record of B-symptoms. Clinically significant differences were also found in pain (10.6 points) and appetite loss (11.7 points).
Table III: Mean EORTC QLQ-C30 health-related quality of life scores at baseline by stage and subgroup compared to the study mean for each domain

<table>
<thead>
<tr>
<th>Stage</th>
<th>Functioning scales</th>
<th>Symptom scales/items</th>
<th>Min. no. any scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physical</td>
<td>Role</td>
<td>Social</td>
</tr>
<tr>
<td>A-progressive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>-2.3</td>
<td>-1.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>Without B-symptoms*</td>
<td>1.2</td>
<td>4.4</td>
<td>4.5</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>4.6</td>
<td>5.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Hb 10-11.9g/dl</td>
<td>-2.7</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Hb ≥12g/dl</td>
<td>7.5</td>
<td>7.5</td>
<td>5.2</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>-4.7</td>
<td>-6.9</td>
<td>-4.9</td>
</tr>
<tr>
<td>Hb &lt;10g/dl</td>
<td>-8.7</td>
<td>-10.8</td>
<td>-5.4</td>
</tr>
<tr>
<td>Hb 10-11.9g/dl**</td>
<td>-2.1</td>
<td>-3.2</td>
<td>-7.3</td>
</tr>
<tr>
<td>Hb ≥12g/dl**</td>
<td>4.7</td>
<td>1.4</td>
<td>-1.1</td>
</tr>
</tbody>
</table>

* Or with no record of B-symptoms (n=5)  ** Platelets <100x10^9/l

>10 points different from the study mean (poorer functioning or more symptoms)
Higher score = better functioning

Higher score = more symptoms

254x148mm (150 x 150 DPI)
254x162mm (150 x 150 DPI)