SPANDIDOS PUBLICATIONS

Transformed follicular lymphoma: The 25-year experience of a UK provincial lymphoma treatment centre

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Abstract. Follicular lymphoma can transform into diffuse large B cell lymphoma, which is usually associated with rapid disease progression, refractoriness to treatment and a poor outcome. We report the 25-year unselected experience of a UK provincial lymphoma treatment centre. This comprises of one of the largest series ever studied. Sixty-three patients were identified (56 initially presented as follicular lymphoma, 5 with 'transformed' lymphoma and 2 with follicular and transformed lymphoma from different biopsy sites). The median age at presentation was 54 years (range 32-76). The median time to transformation was 43 months (range 0-172). For all patients, the median overall survival was 76 months (range 8-254) and from transformation 10 months (range 1-166); 46 of 63 patients have died. For those whose transformation was initially treated with CHOP chemotherapy 10 were in complete remission (CR) and 14 were deceased (median survival 24, range 2-114 months). Five patients had high-dose chemotherapy and 3 were alive (at 25, 36 and 137 months). We conclude that CHOP chemotherapy (probably with rituximab) is a reasonable first treatment in fit patients and high dose chemotherapy with autologous stem cell support deserves further study.

Introduction

Follicular lymphoma is regarded as a low grade (indolent) lymphoma with a clinical course characterised by repeated relapse and remission. This course can be interrupted by histological transformation, usually to diffuse large B cell lymphoma (DLBCL). Transformed lymphoma may be present at initial presentation or may develop during the course of the disease. It is most often seen at the first progression (1) and most commonly presents as a rapidly growing lymph node (2). It may be presented as a more widespread organomegaly or extranodal disease (2). Transformation is usually associated with rapid progression of the disease, with a reduced response to chemotherapy and a poor outlook.

Retrospective studies have shown that transformation occurs in 12-70% of patients over a range of years (3,4). Variable rates may be reported because of differences in re-biopsy rates, the inclusion or not of autopsy results and the length of follow-up. Some studies have only included cases with a histological confirmation whereas others have included cases based on clinical features (5).

Various studies have looked at features associated with an increased risk of transformation. Recently Giné *et al* found that the Follicular Lymphoma International Prognostic Index and grade 3 histology were significantly associated with transformation (6).

Reported overall survival varies between series and depends on which patients are studied. Transformed cases have a comparatively poor survival from the time of transformation (7-9) and from initial diagnosis (2). Overall survival is significantly worse when compared with *de novo* DLBCL (10). Whilst this is the case, there are still some patients who will experience prolonged disease-free survival following transformation, particularly following autologous transplantation (11). Some retrospective studies have looked for factors influencing survival following transformation. Favourable features include the absence of B symptoms and localised disease (12). Those relapsing after treatment for transformed disease have been seen to relapse as both indolent and transformed disease (12).

Materials and methods

Patients were identified via the Weston Park Hospital lymphoma database. Information was extracted from this database and the hospital notes. Each of the patients had their biopsies reviewed by the local specialist lymphoma pathology panel. A diagnosis of high grade transformation was accepted only on the basis of histology or cytology. Clinical diagnosis of transformation was not accepted.

Initial factors that were evaluated included age, gender, performance status, Ann Arbor stage, B symptoms, haemoglobin, platelet count, serum albumin, serum LDH, serum ß$_2$-microglobulin, number of nodal areas, splenic involvement, bone marrow involvement and extranodal involvement. Treatment factors that were evaluated included initial and subsequent treatments and the response to each

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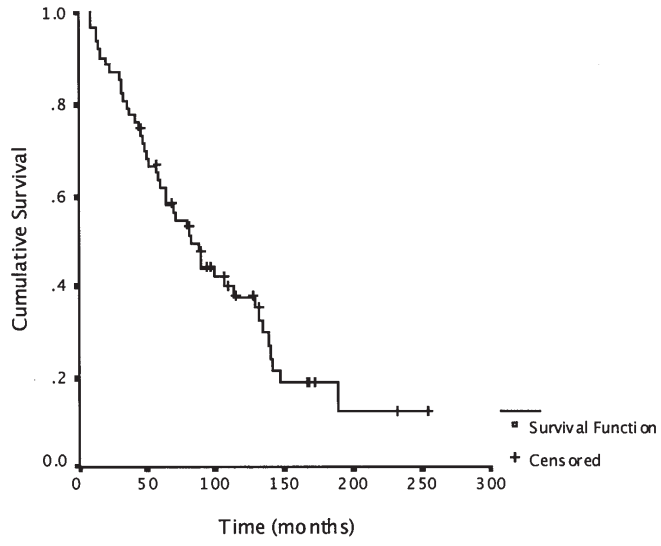

Figure 1. Cumulative survival from diagnosis.

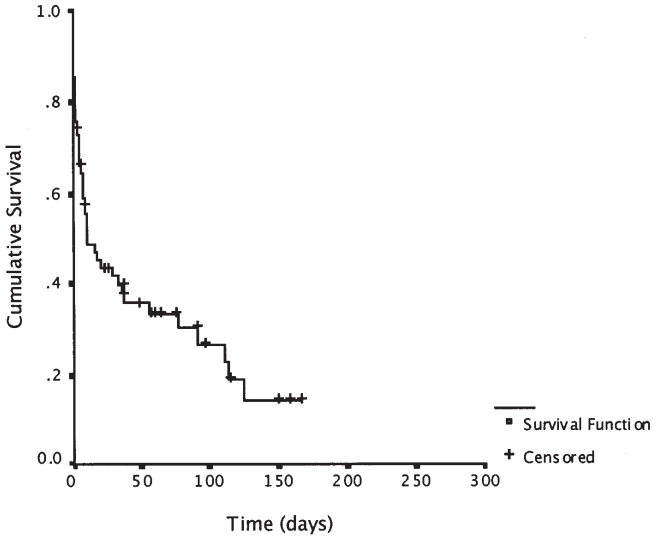

Figure 2. Cumulative survival from transformation.

treatment (complete response, partial response, stable disease and progressive disease). Follow-up data included the length of follow-up, current status (alive in clinical remission, alive with asymptomatic disease, alive with active disease or dead), time to death and cause of death (lymphoma related or not).

Overall survival was calculated from either the date of initial diagnosis (Fig. 1) or the date of transformation (Fig. 2) to either the date of death or the most recent follow-up. Survival curves were performed using Kaplan-Meier survival analysis using software SPSS 11 for MAC OS X.

Results

Patient characteristics. Sixty-three patients were identified, initially presenting over a 25-year period between 1st January 1980 and 31st December 2004 (Table I). They consisted of 31 males and 32 females. The median age at presentation was 54 years (range 32-76 years). At presentation 23 were aged >60 years.

Table I. Initial characteristics.

Parameter	Number of patients (%)
Median age (range)	54 years (32-76)
Gender	31M:32F
Ann Arbor stage	
I	13 (21%)
II	11 (17%)
III	12 (19%)
IV	27 (43%)
'B' symptoms	14 (22%)
Median number of nodal areas (range)	3 (0-9)
Extranodal sites	
None	31 (49%)
1 site	23 (37%)
2 or more sites	9 (14%)
Bone marrow involvement	23 (37%)
Splenic involvement	12 (19%)
Haemoglobin <12.0 g/dl	7 (11%)
Platelet count $<140x10^9$/l	4/52 (8%)
Serum LDH >450 IU/l	7/39 (18%)
Serum albumin <40 g/l	8/44 (18%)

Table II. Median survival following transformation. A comparison of previous studies.

	No. of patients	Median survival (months)
This report	63	10
Acker *et al* (13)	23	8.5
Armitage *et al* (10)	15	12
Bastion *et al* (1)	52	7
Ersboll *et al* (7)	23	4
Gine *et al* (6)	30	14
Hubbard *et al* (8)	23	11
Montoto *et al* (14)	88	14
Ostrow *et al* (9)	11	17
Oviatt *et al* (2)	13	2.5
Yuen *et al* (12)	74	22

Fifty-six initially presented with follicular lymphoma, 5 with transformed disease subsequently relapsing as follicular lymphoma and two with both, having DLBCL involving the lymph gland and follicular lymphoma involving the bone marrow. Sixty patients transformed to DLBCL and 3 were labelled as having Burkitt-like lymphoma.

en patients presented with stage I disease (1A=11, 11 stage II, 12 stage III and 27 with stage IV. There was extranodal involvement (including bone marrow) at presentation in 21 patients and the presenting site was extranodal in 10. The median time to transformation was 43 months (range 0-172 months) for all patients.

Prognostic factors. Adverse prognostic factors according to the Follicular Lymphoma International Prognostic Index (FLIPI) were age >60=23, nodal areas >4=20, Stage III, IV disease=39, Hb <12=7 and LDH >450 IU/l=7 (data not available in 25). Thirty-four patients were in the low risk group at presentation, 18 in the intermediate group and 11 in the poor risk group.

Initial treatment. For those presenting with follicular lymphoma, first treatment had consisted of chlorambucil in 21, radiotherapy in 18 and combination chemotherapy in 16 patients (CHOP in 4, COP in 5 and fludarabine based in 7). Those who initially presented with transformed disease were treated with anthracycline containing combination chemotherapy in 4 and radiotherapy alone in 3.

Treatment of transformation. At transformation, the median number of prior therapies was 2 (range 0-7). Initial treatment of transformation consisted of CHOP chemotherapy in 24 patients, radiotherapy in 7, other combination chemotherapy in 10 (PMitCEBO 3, COP 2, VEDEX 3, PACEBOM 1, VAPEC-B 1), more intensive chemotherapy in 5 (ESHAP 3, IVE 2) and oral chlorambucil in 3 patients. Five patients received high-dose chemotherapy (BEAM) with autologous stem cell rescue. Thirteen patients did not receive treatment for transformation.

Outcome. At the time of writing, 46 patients were deceased, 15 were alive and in clinical remission (range 9-166 months) and 3 were alive with active disease. From diagnosis, the median overall survival was 76 months or 6.3 years (range 8-254 months) and from transformation median overall survival was 10 months (range <1-166 months).

Thirteen patients did not receive treatment for transformation and they had a median survival of <1 month. The three patients who transformed to Burkitt-like lymphoma also had a median survival of <1 month.

For those whose transformation was initially treated with CHOP chemotherapy (n=24), 10 were alive and were in clinical remission and 14 were deceased. The median survival for this group of patients was 24 months (range 2-114 months). Five patients received high-dose chemotherapy (BEAM) with autologous stem cell support following transformation. Two subsequently were deceased from progressive disease and three remained in remission at 25, 36 and 137 months.

Discussion

The data represent the unselected 25-year experience of a UK provincial lymphoma treatment centre in managing patients with follicular lymphoma, who have had aggressive histological transformation. The patient group is broadly similar to previously described groups in terms of age, gender distribution and distribution of initial stage (1,6,12). It is similar in terms of outcome (Table II). Previous reports of transformation have differed in their inclusion criteria; some studies have included autopsy data, while others have included patients on cytological grounds (6) and others on clinical features (5). Including patients solely on the basis of histological grounds does make the diagnosis more accurate though probably underestimates the true incidence. Rebiopsy rates and policies also vary between studies. Whilst the aim may be to re-biopsy patients at each episode of disease progression, in practise this is unlikely to be achieved. Assessing the extent of transformed disease is also not straightforward; it is neither feasible nor practical to biopsy all disease sites at relapse. This is particularly relevant when considering the role of radiotherapy in treating transformed disease.

There is very little published on the treatment of transformed follicular lymphoma and therefore deciding on the optimal evidence based treatment is difficult. The authors are unaware of any prospective trials exclusively for transformed follicular lymphoma. The most specific publications report on autologous transplantation with encouraging results. However, these series are likely to represent highly selected groups of patients and the majority of patients with transformed follicular lymphoma are likely either to be too old or too unwell or to have had an insufficient response to re-induction chemotherapy. Included in this series are 24 patients who were treated with CHOP chemotherapy. They had an overall response rate of 63% (CR 42%, PR 21%). Overall, this group had a median survival of 24 months (range 2-114 months) whilst those attaining a CR had a median survival of 62 months. These results may be improved with the addition of rituximab. We propose that CHOP (with or without rituximab), is a reasonable choice for the treatment of transformed follicular lymphoma and that a prospective trial is much needed. With an overall median survival of just 10 months, this study is a reminder of the seriousness of transformation.

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