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Lack of effectiveness of routine clinic and blood test-based follow-up for diffuse large B cell lymphoma

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The optimal approach to surveillance following remission with first line therapy for diffuse large B cell lymphoma (DLBCL) remains controversial with a paucity of evidence whether follow up is effective in early relapse detection, role of blood tests, optimal frequency and duration of follow up, and little data in the modern rituximab era (Cohen*, et al* 2015). There is no guideline consensus. British Society of Haematology guidelines in 2016 recommend clinical follow up for two years followed by discharge, based on the observation that <10% of patients relapse after more than two years (Chaganti*, et al* 2016). The National Institute of Clinical Excellence (NICE) guidelines in 2016 recommend follow up for three years (National Institute of Clinical Excellence). By contrast, the 2014 Lugano consensus recommends longer follow up, 3 monthly for 2 years, 6 monthly for 3 years and then annual follow up (Cheson*, et al* 2014). We have evaluated the approach in our centre in the rituximab era with clinical follow up for at least 5 years with routine blood tests including lactate dehydrogenase (LDH) without routine imaging.

Patients with DLBCL treated in the Leeds Cancer Centre between 2006-2014 were retrospectively identified. Criteria for inclusion were: age >18 at diagnosis, pathological diagnosis of DLBLC, curative intent treatment with rituximab and anthracycline-containing chemotherapy, response consistent with remission. Exclusion criteria were: palliative treatment including attenuated chemotherapy, transformed indolent lymphoma, concurrent low grade lymphoma, CNS disease. Standard follow up schedule was: clinic 3 monthly for 1 year, 4 monthly for 1 year, 6 monthly for 3 years, option of discharge or annual follow up, with a bloods including LDH at each appointment. Imaging was not routinely performed, although occasionally at clinician discretion. Relapse was categorised as symptomatic (including patient-detected lymph nodes) or asymptomatic (including abnormal examination findings not been noticed by the patient). Methods of relapse detection were categorised: patient reported at routine clinic, clinical examination at routine clinic (abnormality not reported by patient), detection via routine clinic blood tests, early clinic visit, routine imaging, other route (e.g. Accident and Emergency (A&E) department attendance, via General Practioner (GP)).

185 patients were identified who entered routine follow up. Patient and treatment characteristics are shown in Supplementary Table 1. Median follow-up was 57.2 months (range 5.9-109 months). Two and five year relapse-free survival and overall survival were 87.4%, 84.6% and 90.2%, 79.5% respectively. 30/185 (16.2%) of patients relapsed during follow up. 7/30 (23%) of relapses were in patients with stage I/IIA disease. Median time to relapse was 16 months post diagnosis. 23/30 relapses (77%) occurred within 24 months of diagnosis.

Regarding relapse presentation, 26/30 (87%) were symptomatic at time of relapse. Of these, 10 presented with pain, 7 with a new patient-detected lump, three with CNS symptoms, and one each with lethargy, dyspnoea, ascites, increased sweating, weight loss and a dermatological lesion. Table 1 summarises the method of relapse detection. 10/30 (33%) relapses were via self-reports at routine clinic appointments and 8/30 (27%) self-reports between clinics (via a telephone call from patients regarding new concerning symptoms, prompting unscheduled clinic assessment). 3/30 (10.0%) relapses were identified after a GP referral and 5/30 (16.7%) as the result of attendance at an A&E department. 4 patients who had a relapse detected were asymptomatic and did not report any concerns. This included two patients had abnormal lymph nodes detected at routine clinic examination. One patient had pancytopenia detected on a routine bloods 12 months post treatment at follow up; this patient had bone marrow disease at presentation. One patient had relapse identified on a CT scan repeated 3 months following post-treatment imaging in view of a complete response uncomfirmed. Overall, 16/30 (53.3%) relapses were identified outside routine clinical follow up appointments. Figure 1 summarises methods of relapse detection.

These data show that this clinically based follow up schedule incorporating regular blood monitoring was ineffective at detection of asymptomatic disease recurrence. The pattern of the majority of relapses occurred early is consistent with other series (El-Galaly*, et al* 2015, Thompson*, et al* 2014). A large majority of relapses were detected via symptomatic presentation, consistent with reports of clinical follow up programmes pre-rituximab (Elis*, et al* 2002, Weeks*, et al* 1991). Despite a frequent schedule of routine clinic visits/blood

monitoring, most patients with relapse presented between regular clinic intervals, with a majority (53%) of relapses detected via either unscheduled appointments or GP/A&E visits.

Routine blood monitoring led to the detection of relapse in a single asymptomatic patient in this series. There were no cases of asymptomatic relapse detection based upon LDH elevation. A study in the pre-rituximab era (Weeks*, et al* 1991) led to the widespread implementation of LDH in routine surveillance. However, it has been shown that most patients with relapse preceded by an LDH elevation also have symptoms (El-Sharkawi*, et al* 2012), and that a raised LDH has limited sensitivity (44-69%) and poor positive predictive value (9-38%) (Cheah and Seymour 2014). The lack of utility of routine blood tests, including LDH, in our series suggests that routine blood monitoring has little value.

The question of whether it is feasible to detect early asymptomatic recurrence should underpin the design of evidence-based follow up programmes. Imaging surveillance is not recommended (Cheson*, et al* 2014); in studies with CT or PET, the majority of relapses were identified symptomatically outside of the timeframe of scheduled visits with no survival benefit (El-Galaly*, et al* 2015, Thompson*, et al* 2014). DLBCL relapse is generally aggressive with rapidly developing symptoms. Rapid disease progression translates into a short lead time for preclinical diagnosis. This is reflected in our results with the observation of a very high proportion of relapses being symptomatic and often detected at unscheduled visits or via other healthcare routes, with the use of routine bloods being ineffective. These data suggest that follow up programmes should be reconfigured to improve responsiveness to patient reported symptoms. Long term routine face-to-face clinic follow up of asymptomatic patients is of little value, and early discharge with education and rapid clinic access for re-evaluation can be recommended.

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Figures

Figure 1: Pattern of relapse detection over time. Relapses detected via routine clinic follow up (blue) and outside of routine clinic follow up (red).

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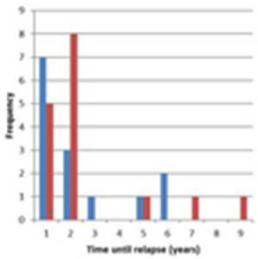

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Table 1: Method of relapse detection

Method of relapse detection	Overall	Relapse within 2 years of diagnosis	Relapse after 2 years of diagnosis
Patient self-reporting between routine clinics	8	6	2
Patient self-reporting at routine clinics	10	7	3
Clinical examination during routine clinics	2	1	1
Routine blood tests	1	1	0
Routine radiological investigations	1	1	0
GP referral	3	3	0
A&E admission	5	4	1

Supplementary Table 1: Patient, disease, treatment characteristics of patients entering routine follow up

	n (total =185)	%
Age (years):		
Mean	62	
Median	65	
Range	20 – 91	
Sex:		
Male	109	58.9
Female	76	41.1
Stage:		
Stage IA/IIA:	76	41.1
Stage IA	38	20.5
Stage IIA	38	20.5
Stage IB/IIB/III/IV:	109	58.9
Stage IB	2	1.1
Stage IIB	6	3.2
Stage IIIA/IIIB	26	14.1
Stage IVA/IVB	75	40.5
B symptoms	37	20.0
Extranodal	30	16.2
Treatment regimen:		
R-CHOP	179	96.8
R-CODOX-M/IVAC	6	3.2
All patients:		
3 x R-CHOP + radiotherapy	19	10.3
6-8 x R-CHOP	109	58.9
6-8 x R-CHOP + radiotherapy	27	14.6
<6 x R-CHOP*	24	13.0
R-CODOX-M/IVAC	6	3.2
Response assessment:		
CT	131	70.8
PET	46	24.9
Other**	8	4.3

*Planned for 6-8 x R-CHOP but stopped early due to toxicity (8 with stage I/IIA disease).
**No radiologically assessable disease (either excised at diagnosis or detectable by endoscopy only)