Chapter 4

Survival of transformed follicular lymphoma (TFL) in the rituximab era; an analysis from the Population based Haematological Registry for Observational Studies (PHAROS) in the Netherlands.

MJ Wondergem1*, DE Issa2*, JM Zijlstra3, O Visser3, HM Blommestein3,4, PC Huijgens3, BI Witte5, MED Chamuleau1, S Zweegman1.

1Department of Hematology, VU University Medical Center
2Department of Hematology, Jeroen Bosch Ziekenhuis
3Netherlands Comprehensive Cancer Organization (IKNL)
4Department of Health Policy and Management, institute for Medical Technology Assessment, Erasmus University Rotterdam
5Department of epidemiology and biostatistics, VU University Medical Center
*:equally contributed

Submitted for publication
Abstract

**Purpose** First-line treatment for TFL is diverse and the value of autologous stem cell transplantation (ASCT) is unknown. To obtain insight in treatment and survival of TFL patients, we analyzed patients registered in the Population based Haematological Registry for Observational Studies (PHAROS) comprising 40% of the Netherlands.

**Patients and methods** Patients with follicular lymphoma (FL) registered between January 2004 and July 2013 who were also diagnosed with diffuse large B cell lymphoma (biopsy proven) were selected. Overall survival (OS) was analyzed in subgroups for age and treatment.

**Results** 152 of 161 included patients received rituximab chemotherapy (R-chemo) as induction for TFL, being successful in 97 patients; 64 received R-chemo only, 32 received up-front ASCT, 1 allo-SCT. Two-year OS of all patients was 55%, being significantly worse > 65; 41% vs 62%. Patients non-refractory to induction (69% > 65 and 60% ≤ 65) had a 2-year OS of 60% and 88% after R-chemo only (96% after up-front ASCT) respectively. Significantly more patients previously treated for FL underwent up-front ASCT. 55 patients were refractory (34%). Salvage ASCT, feasible in 15 patients, resulted in a 2-year OS of 40% versus no survival without ASCT.

**Conclusion** Two-year OS of all patients was 55%. Patients ≤ 65 years after successful induction had the best 2-year OS: 88% after R-chemo only, 96% with up-front ASCT, both with long term survival. Our data suggest up-front ASCT might overcome the negative effect of previous FL treatment. In refractory patients only salvage ASCT offers long term survival.
Introduction

Transformation of follicular lymphoma (FL) to a high-grade aggressive non-Hodgkin lymphoma (mostly diffuse large B cell lymphoma, DLBCL) occurs in approximately 3% of patients per year. In the pre-rituximab era, transformation had a pronounced negative impact on overall survival (OS), with a median OS ranging from 0.6-2.7 years only (1-7). Autologous stem cell transplantation (ASCT) was introduced to improve survival after chemotherapy only and resulted in 5 yr OS of 40-60% (8-10). This prompted many centers to adopt up-front ASCT for the treatment of TFL patients. However, in the era of rituximab the role of up-front ASCT is subject to debate. The introduction of rituximab to TFL treatment has improved survival considerably, with a median OS of around 50 months described in patients after R-chemo with or without ASCT or allogeneic stem cell transplantation (11-13). Two large cohort studies reported a significant, but only slightly improved OS after up-front ASCT (Ban hoeffen 2 yr OS 74% vs 59%, Da villa 5 yr 65% vs 61%). Since there is a lack of randomized clinical trials to guide clinical decision making, the optimal treatment of TFL is unknown. As a consequence the choice of treatment is based on criteria like local policy, previous treatment for FL, comorbidity and performance status of the patient. To obtain insight in the treatment of patients with TFL in the Netherlands and its resulting survival, we analyzed patients registered in the Population based Haematological Registry for Observational Studies (PHAROS).

Patients and methods

Disease and treatment data
Data were obtained from the nationwide Netherlands Cancer Registry (NCR) and PHAROS. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated national pathological archive (PALGA, “Pathologisch Anatomisch Landelijk Geautomatiseerd Archief”), as well as hospital discharge registries. The NCR collects data such as date of birth, gender, date of diagnosis, morphology (ICD-O-3), Ann Arbor stage, B symptoms and primary treatment from medical records (14). Information on date of death is actively obtained from the municipal registries and from the database of deceased persons of the Central Bureau for Genealogy and the municipal civil registries (GBA).

In addition to the NCR data, PHAROS, a population based registry, records data on comorbidities, investigations performed, performance status, LDH, hepato-or-splenomegaly...
and peripheral blood count at diagnosis. Data recorded at start of every new treatment line were date, Ann Arbor stage, performance status, LDH and blood count, specification of type of treatment, substances and/or doses used, remission status. PHAROS covers 40% of the Dutch population and is located in the north-west and south-west of the Netherlands.

Patient selection
For this analysis, all patients registered between January 2004 and July 2013 with FL who were diagnosed with DLBCL during the course of their disease were selected. TFL was defined as a biopsy proven diagnosis of DLBCL in a patient with underlying FL in a lymph node, previously or simultaneously diagnosed. Patients with a FL component in the bone marrow only, without a biopsy proven diagnosis of FL in a lymph node, were not included.

Statistics
Data were analyzed using the SPSS statistical package (IBM version 20.0). Differences between treatment groups were compared using the Chi-square for categorical variables and Kruskal Wallis test for medians. Overall survival (OS) was calculated from the date of diagnosis of transformation until death from any cause or patients were censored at date of last follow up. OS was estimated using the Kaplan-Meier method and differences were compared using the log rank test. Time to next treatment (TTNT) was calculated from the date of remission after induction until date of next treatment. With the use of univariate analysis (log rank test) the following prognostic factors were analyzed: age, gender, time to transformation (≤18 months and >18 months (11)), stage and LDH at diagnosis of TFL, previous treatment for FL, previous R for FL, number of treatment lines for FL, type of treatment for TFL. Prognostic factors with a univariate p-value <0.1 were included in a multivariable cox regression model and selected via a forward selection procedure (p-value<0.05 for entry).
Table 1: patient characteristics

<table>
<thead>
<tr>
<th>Patients &lt;65 years</th>
<th>R-chemo n=28 (29%)</th>
<th>Up-front ASCT n=30 (31%)</th>
<th>Salvage ASCT n=15 (16%)</th>
<th>Refractory n=23 (24%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transformation in years (range)</td>
<td>57 (34-65)</td>
<td>58 (35-65)</td>
<td>58 (35-65)</td>
<td>61 (42-65)</td>
</tr>
<tr>
<td>Median time to transformation in months (range)</td>
<td>9 (0-85)</td>
<td>19 (0-84)</td>
<td>7 (0-79)</td>
<td>11 (3-52)</td>
</tr>
<tr>
<td>male/female</td>
<td>13/15</td>
<td>13/17</td>
<td>7/8</td>
<td>14/9</td>
</tr>
<tr>
<td>Number of treatment lines for FL</td>
<td>0</td>
<td>17</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>14</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>2-4</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Previous treatment for FL any therapy*</td>
<td>11</td>
<td>20 **</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>R-chemo</td>
<td>7</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stage at transformation</td>
<td>1-2</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>3-4</td>
<td>24</td>
<td>25</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>13</td>
<td>11</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Treatment for TF</td>
<td>R-CHOP</td>
<td>26</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>R-DHAP</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>R-PECC</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ASCT preceded by Z</td>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients &gt;65 years</th>
<th>R-chemo (n=38)*</th>
<th>Refractory (n=17)</th>
<th>No treatment (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transformation (range)</td>
<td>73 (66-81)</td>
<td>73 (66-87)</td>
<td>80 (66-91)</td>
</tr>
<tr>
<td>Median time in months to transformation (range)</td>
<td>23 (0-88)</td>
<td>17 (1-101)</td>
<td>21 (2-57)</td>
</tr>
<tr>
<td>Male/female</td>
<td>20/18</td>
<td>8/9</td>
<td>2/7</td>
</tr>
<tr>
<td>Number of treatment lines for FL</td>
<td>0</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2-4</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Previous treatment for FL any therapy***</td>
<td>21***</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>R-chemo</td>
<td>12</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Stage at transformation</td>
<td>1-2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3-4</td>
<td>34</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>16</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Treatment for TF</td>
<td>R-CHOP</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>R-DHAP</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>R-PECC</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*any therapy=chemo only or R-chemo or RT
**including antracyclines in three patients
***including anthracyclines in two patients
12 patients were treated with up-front consolidation with ASCT
R-CHOP=rituximab, cyclofosfamide, doxorubicine, vincristine, prednisone
R-DHAP=rituximab, dexamethasone, high dose ara-c and cisplatinum
R-PECC=rituximab, lomustine, etoposide, chlorambucil, prednisone
Z=90Yttrium ibritumomab tiuxetan
Chapter 4

Results

Patient characteristics

161 patients were selected out of 1542 registered patients with FL. For all TFL patients the median age at transformation was 63 years (range 34-91). The median time from diagnosis of FL to transformation was 14 months (0-101 months), median follow-up was 17 months (1-111 months).

Sixty-two percent of patients (99/161) had previously received treatment for FL: 90 had been treated with chemotherapy, of whom 72% (65/90) with R-chemo. Nine patients had received radiotherapy only. In 37 patients (23%) a watch and wait policy was followed, therefore they did not receive therapy for FL, and in 25 patients (15%) FL and DLBCL were diagnosed simultaneously.

Figure 1: Overall survival in all TFL patients.

Outcome of all TFL patients

Median OS of all 161 TFL patients was 52 months, with a 2 year OS of 55% (95% CI 47-63%, figure 1). When only considering patients who were treated for TFL (n=152), 2 year OS was 60%. Patients who were sensitive to induction therapy had a significantly better 2 year OS than patients who were refractory to induction R-chemo (83% versus 13% (p<0.001)). Patients ≤ 65 years had a significantly better OS than patients > 65 years (2 year OS 62% vs 41%, p=0.003). Therefore, we performed a separate analysis of the 97
patients of 65 years and younger and the 64 patients older than 65 years to determine the effect of treatment on outcome.

Five patient groups were defined: a) successful induction with R-chemotherapy only: R-chemo group, b) successful induction with R-chemotherapy followed by upfront ASCT, with or without Yttrium ibritumomab tiuxetan (Z): up-front ASCT group, c) failed induction with R-chemotherapy but able to undergo ASCT, with or without Z: salvage ASCT group, d) refractory to all therapies, i.e. failed induction and unable to undergo ASCT: refractory group and e) no treatment: no treatment group. In general, in patients >65 years, both up-front and salvage ASCT are not considered. Indeed, ASCT was not performed, except for 2 patients. Patient characteristics per treatment group and stratified by age are depicted in table 1.

**Outcome in patients ≤ 65 years**

All 97 treated patients received R-chemo as induction treatment: 28 patients (29%) received R-chemotherapy only, 30 (31%) were in remission after induction R-chemo and received up-front ASCT (all with BEAM conditioning, 23 preceded by R, 9 preceded by Z). Only 1 patient received up-front consolidation with allogeneic SCT and therefore was not included in the survival analysis. 38 (40%) patients were primary refractory to induction treatment, of whom 15 received ASCT after salvage R-chemotherapy and 23 patients were refractory even to salvage R-chemotherapy (figure 2). When patients had previously been treated for FL, up-front ASCT was offered significantly more often as treatment for TFL compared to previously untreated patients (65% vs 37%, p=0.037).
In patients who reached CR after induction with R-chemo only, 2 year OS was 88% (95% confidence interval (CI): 75-100%). In patients who subsequently underwent an ASCT this was 96% (95% CI:89-100%, p=1.0 after Bonferroni correction).

Two year OS was 40% in the 15/38 patients who were refractory to R-chemo but could eventually be salvaged with ASCT (95% CI:15-65%). In seven of these 15 patients CR was reached following re-induction, resulting in a superior 2-year OS of 86% versus 25% in patients reaching SD or PR only before a salvage ASCT. In the 23 R-chemo refractory patients who were unable to reach salvage ASCT no long term survival could be reached (2 year OS 0% (figure 3)).
Survival of transformed FL in the Netherlands

Figure 3: Overall survival and time to next treatment (TTNT) per type of TFL treatment in patients ≤ 65 years (p<0.001 for both).

Two year treatment free survival was 66% in the R-chemo group (95% CI: 47-85%), 90% in the up-front ASCT group (95% CI: 77-100%) and 33% in the salvage ASCT group (95% CI: 9-57, p<0.001, figure 3). TTNT was not significantly different between the up-front ASCT group and the R-chemo group (p=0.11 after Bonferroni correction)
Outcome in patients > 65 years
Nine out of 64 patients did not receive any therapy. The 55 patients who received R-chemotherapy reached a 2 year OS of 65% after successful R-chemo induction (38/55 patients, 95% CI: 46-84%), and 8% when primary refractory (17/55 patients, 95% CI: 0-22%, p<0.001, figure 2 and 4).
Patients > 65 years had significantly worse OS than patients ≤ 65 years after successful induction with R-chemo (p<0.001), and outcome was also significantly worse when only considering the patients without up front ASCT (p<0.010).

Figure 4: Overall survival per TFL treatment group in patients > 65 years.

Predictors of survival
In a univariate analysis we identified the following variables having prognostic significance for overall survival: age at diagnosis of TFL (≤ 65 years vs > 65 years, p=0.003), elevated LDH at diagnosis (p<0.001), previous treatment for FL (p=0.018), number of treatment lines for FL (p=0.043), all inversely associated with survival. Early versus late (≤ 18 versus > 18 months after diagnosis of FL) transformation did not have a significantly different OS (figure 5).
In a multivariable cox regression model, LDH at diagnosis was the most significant predictor of survival (p<0.001), followed by previous treatment for FL (p=0.012) and age at diagnosis of TFL (p=0.011).
Survival of transformed FL in the Netherlands

Discussion

Since patients with TFL are often excluded from clinical trials, objective data to guide therapy in general practice are lacking. Therefore, registry and cohort study analyses are currently the most useful source of information on the treatment of TFL in first line. We here present the treatment and outcome of a large cohort of 161 TFL patients from the Dutch population based registry PHAROS.

In accordance to what has been reported in literature our population based registry showed that in general, outcome of TFL in the rituximab era is still poor with a 2 year OS of 55% only (11-13,15). However, by having access to detailed treatment data we were able to identify a subgroup of patients with a good prognosis. Although in patients

Figure 5: Predictive factors for survival
>65 years, 69% reached a CR after induction, 2 year OS was 65% only. However, in approximately 60% of patients ≤65 years, CR could be reached with R-chemotherapy, resulting in a 2 year OS of 88% without up-front ASCT and 96% after up-front ASCT, with an apparent plateau in survival. This is considerably better than the data reported by Ban Hoeffen and Da Villa and colleagues (2 year OS 59% and 68% after R-chemo only, respectively). This might be caused by the presence (percentage not given) of refractory patients in the R-chemo group in their series as OS is dismal in case of refractoriness. In addition, the inclusion of patients >65 years probably plays a role in the study of Ban Hoeffen, since 2 year OS increased to 59% in a subgroup analysis they performed ≤60 years, similar to our series (2 year OS 62% patients ≤65 years vs 41% in patients >65 years) (12,13).

From our series it cannot be stated that up-front ASCT improves survival, as OS was found not to be significantly different from OS after R-chemo only. This might be due to small numbers. However, there might also be a bias due to the fact that for up-front ASCT a patient population with more high risk disease was selected, supported by the significantly higher percentage of patients being previously treated for FL (65 vs 37% in the patients with R-chemo only, p=0.037). It is known that patients who previously have needed treatment for FL have a worse outcome after transformation than treatment naïve patients (6,11,13,15). Accordingly, previous treatment for FL was a main negative prognostic factor for survival in our multivariable analysis.

The similar OS after successful R-chemo irrespective of up-front ASCT might indicate that up-front ASCT did overcome the negative effect of being treated previously for FL. This has also been observed by others (13). When anthracyclines were used in previous treatment for FL, even improved OS has been observed in patients receiving up-front ASCT compared to R-chemo only (12,15). Therefore, based on these and our data, in clinical practice up-front ASCT should be considered in patients who were previously treated for FL, especially when anthracyclines were included (4).

Not surprisingly, patients who failed induction R-chemotherapy (34% of all TFL patients) had a poor outcome. We here show a clear role for ASCT as salvage therapy obtaining a 2 year OS of 40% versus no long term survival in those patients in whom a ASCT was not possible. Unfortunately, only 40% of primary refractory patients ≤65 years were able to undergo salvage ASCT. Moreover, half of the patients reached less than CR before ASCT, with only 25% of patients being alive at 2 years. Whether radioimmunotherapy (Z) added to ASCT improves the poor outcome in these primary refractory patients is
unclear and numbers in this analysis are too low to draw conclusions. However, the addition of Z to conditioning for ASCT is feasible and has shown promising results in TFL in first and second line (16,17). Considering its effectiveness in both FL and DLBCL, also for chemo-sensitive patients, it is not unreasonable to expect benefit in the treatment of TFL, although for salvage, higher doses of Z might be needed (18-20).

In our series, 38 patients were refractory to any treatment (25%), a percentage that is comparable to what has been reported in literature (21,22). The lack of long term survival we and others found in these patients (5,6) indicates the urgent need for therapies other than R and/or chemotherapy or radiotherapy. Encouraging overall response rates of 45-60% have been reported with lenalidomide (23-25). Other promising drugs, such as compounds targeting PD-1 ligand, aurora A kinase, bruton tyrosine kinase and PI3Kinase are currently studied in indolent and aggressive lymphomas and will hopefully also be of value in TFL (26-29). A more refined approach would be to define new targets by performing genetic analyses, to find specific mutations and overexpression of genes in TFL that might explain the extreme refractoriness of this disease (30). For example, the elevated LDH we found to be associated with refractoriness and consequently outcome (present in 42% of chemosensitive and 70% of refractory patients) might be a derivative of pro-proliferative changes in the TFL like myc up-regulation, known to occur in TFL and not in FL. In the future, these genetic analyses might be used to identify mechanisms of resistance in individual patients, guiding their treatment.

Conclusion

Our Dutch PHAROS population based registry data reveal that when treatment with R-chemotherapy resulted in remission, subsequent 2 year OS was 83%. Patients > 65 years had a 2 year OS of 65% after successful induction. Patients ≤ 65 years did significantly better, reaching a 2 year OS of 88% after successful induction with R-chemo only and 96% when R-chemo was followed by consolidation with an up-front ASCT, with long term survival. Moreover, our data suggest that up-front ASCT might overcome the negative effect of previous need for treatment of FL. However, prospective studies are needed to identify the patients benefitting most of up-front ASCT. Unfortunately, there is a high rate of refractoriness to induction therapy (34%) with a dismal outcome. For these patients salvage therapy with ASCT is the only chance for long term survival. Unfortunately, this is possible in only 27% of refractory patients, indicating a high unmet need for novel therapies.
References

5. Gine E, Montoto S, Bosch F et al. The Follicular Lymphoma International Prognostic Index (FLIPI) and the histological subtype are the most important factors to predict histological transformation in follicular lymphoma. Ann Oncol. 2006;17(10):1539-1545
Survival of transformed FL in the Netherlands