Improved survival for non-Hodgkin lymphoma patients in New South Wales, Australia

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Abstract

Background

We evaluated if the survival benefit of adding rituximab to standard chemotherapy for non-Hodgkin lymphoma (NHL) observed in clinical trials has been experienced by an Australian NHL patient population.

Methods

NHL cases diagnosed in 1990-2004 in New South Wales (NSW) were followed-up to the end of 2004. Rituximab prescription data were obtained from Medicare Australia. Excess risk of death due to NHL in 1990-1994, 1995-1999 and 2000-2004 was compared using Poisson regression models. Trends in incidence and mortality were also estimated.

Results

Compared with cases diagnosed in 2000-2004, age and sex adjusted relative excess risk of death was significantly higher in 1990-1994 (2.10) and 1995-1999 (1.82). Further adjustment for NHL subtype reduced the excess risks slightly, but they remained statistically significant. A sharp fall in mortality was observed from 2000 to 2004 (annual percentage change (APC) =-4.7, p=0.009), while a small but significant rise in incidence was seen from 1990 to 2004 (APC=0.5, p=0.01). The number of times rituximab was dispensed in NSW increased rapidly from 1274 in 1999 to 9250 in 2004.

Conclusion

It is likely that some benefit of adding rituximab to the standard chemotherapy for NHL has been experienced at the population level.
Background

The incidence of non-Hodgkin lymphoma (NHL) had increased substantially in recent decades with smaller increases in recent years in many western countries including Australia. The mortality for NHL rose at a similar rate, stabilised in the early 1990s and then started to fall at the end of the 1990s. The survival pattern for NHL had not changed significantly in over two decades up to the late 1990s despite attempts to increase the efficacy of the standard treatment, combination chemotherapy (CHOP), with the addition of other cytotoxic drugs [1]. Two pivotal clinical trials in the late 1990s showed that the addition of the monoclonal antibody targeting the CD20 antigen expressed on almost all malignant B cells, rituximab, to standard chemotherapy regimens improved the survival for patients with indolent NHL, and patients with diffuse large B-cell lymphoma (the two commonest NHL subtypes) [2].

This revolutionary advance in the treatment of NHL was introduced in Australia in around 2000 [3, 4]. The aim of this study was to evaluate if the introduction of this new treatment modality improved the prognosis of NHL patients in the State of New South Wales (NSW), Australia.

Methods

Data

Data were obtained from the population-based NSW Central Cancer Registry, Australia, for cases diagnosed with a single first primary NHL between 1990 and 2004. Based on population size, NSW is the largest state comprising approximately one-third of the Australian population. Notification of cancer has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology departments since 1985 [5]. Coding for primary site and NHL subtype was done
either by medical coders in the hospitals that notified the Registry, or by medical coders in the Registry, who generally assigned subtype based on pathology and hospital notifications. The proportion of cases that were histologically verified has been relatively constant (>85%) since 1985 [5]. Cases aged less than 15 years old, or those reported to the Registry through death certificate only or first identified at post-mortem were excluded. All eligible cases were matched to death records from the State Registrar of Births, Deaths and Marriages and the National Death Index to determine survival status at 31 December 2004.

We obtained the Pharmaceutical Benefits claims data representing the number of times rituximab was dispensed including original prescriptions and repeats [6] in NSW for 1999-2004 from the Medicare Australia website. The prescription codes for NHL patients only were used (8293L, 8294M, 8665C and 8666D), so any increase in the number of claims is directly related to an increase in use for the treatment of NHL. As rituximab was listed for subsidisation in mid 1998, we did not include data for that year.

**Trends in survival**

Relative survival, a means of removing the effect of mortality from other causes [7], was used in this study because causes of death on death certificates are often inaccurate [8]. Relative survival is the ratio of the observed proportion surviving in a group of patients to the expected proportion that would have survived in a comparable group of people (with the same distribution by age and sex) from the general population [9].

The survival time was measured from the month of diagnosis to the date of death or censoring at 31 December 2004, whichever occurred first. The Australian Bureau of Statistics provided all cause mortality data and the NSW population by single year of age, sex and calendar year
for 1990-2004. To analyse trends in relative survival, three time periods were defined: 1990-
increases the likelihood that cancer patients diagnosed within a period followed similar
treatment protocols. For the first two periods (1990-94, 1995-99), relative survival was
estimated using the traditional cohort method, and the period method [10] was used for 2000-
2004 as five-year follow-up was incomplete for this cohort. The period method was used also
to estimate survival during 1995-99 for comparison.

As treatments for NHL depend on histological subtypes [11] and there are approximately 40
different subtypes [12], we grouped all subtypes into four broad groups according to the cell
of origin as well as their response to therapy and overall survival. They are “aggressive B-
cell”, “indolent B-cell”, “other NHL (mainly T/NK cells)” and “NHL not otherwise specified
(NOS)”. The clinical groups were based on the WHO classification for lymphoma [13] and
the International Classification of Disease-Oncology Third Edition (ICD-O-3) [14]. Cases
diagnosed in 1990-2001 were coded according to ICD-O-2 [15] in the registry; a computer
program converted the ICD-O-2 codes into ICD-O-3. Cases diagnosed after 2001 were coded
in ICD-O-3.

Changes in survival over time may be due to several factors, so we assessed the effect of
period of diagnosis on survival using multivariable analysis to adjust for confounding
variables [16]. Briefly, we fitted two statistical models. In the first model, we estimated the
relative excess risk of death (RER) due to cancer in 1990-1994 and 1995-1999 relative to
2000-2004 assuming a Poisson distribution for excess deaths [17, 18]. In the Poisson model,
the dependent variable was the number of excess deaths (calculated as the observed number
of deaths minus the expected number of deaths based on the population death rates) with
explanatory variables being period of diagnosis, age group at diagnosis (15-44, 45-59, 60-74 and 75+ years), sex and year of follow-up, and the natural logarithm of the population size as the offset. The RER derived from this model is the ratio of the excess risk of death in a given period to the reference period of 2000-2004 after controlling for other factors included in the model. A RER greater than one for a given period indicated that the risk in that period was higher than that for 2000-2004 and vice versa. Ninety-five percent confidence intervals (CIs) for the RERs were calculated using the estimated coefficients and standard errors from the Poisson model. A two-sided, log-likelihood ratio test with p<0.05 was taken to indicate statistical significance. In the second model, we estimated RER for each period with additional adjustment for subtypes of NHL to ascertain if differences in subtypes accounted for the effect of period of diagnosis on survival [18].

All analyses were conducted using SAS version 9.0, and the procedure GENMOD was used to fit the models and assess the prognostic effects of the variables on relative survival.

**Trends in incidence and mortality rates**

To estimate trends in incidence and mortality for NHL, which we report as context for the survival trend, annual age-sex standardised incidence and mortality rates were calculated for the NSW resident population for 1990 to 2004. These rates were expressed per 100,000 of the population and age and sex adjusted by the direct method to the 2001 Australian standard population.

Joinpoint regression analysis [19] was used to identify points where a statistically significant change in the trend (linear slope) occurred. The software [20] takes trend data and fits the simplest joinpoint model that the data allows. The analysis starts with the minimum number
of joinpoints and tests whether one or more joinpoints are statistically significant and must be added to the model. In the final model each joinpoint (if any) indicates a statistically significant change in trend, and an annual percent change (APC) is computed for each of those trends. Significant changes include changes in direction in the rate of increase or decrease. Joinpoint software version 3.3 [20] from the US National Cancer Institute was used.

Results

A total of 18,798 NHL cases were included in this analysis, with the commonest subtypes being diffuse large B-cell lymphomas (DLBCL) (5022) followed by small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL) (3929). Table 1 shows the NHL subtypes and main groups and their ICD-O-3 codes. Indolent and aggressive lymphomas accounted for 40.1% and 31.2% respectively. Among indolent lymphomas, SLL/CLL (9670, 9823) was the commonest subtype followed by low-grade follicular lymphoma while DLBCL (9678-9680, 9684) was the commonest aggressive lymphoma subtype. Other types of lymphomas included mainly T/NK-cell lymphomas.

(Insert Table 1 about here)

Table 2 shows the characteristics of the study population by period of diagnosis.

(Insert Table 2 about here)

Relative survival for NHL was substantially higher in 2000-2004 (Figure 1). The difference in five-year relative survival remained statistically significant when the period method was used for 1995-99 (67.6% vs 73.1% in 2000-2004).

(Insert Figure 1 about here)
Five-year relative survival for 2000-2004 was higher for all age groups and for all subtypes except for ‘Other NHL’ (Figure 2).

(Insert Figure 2 about here)

Compared with cases diagnosed in 2000-2004, relative excess risk of death was significantly higher in 1990-1994 (RER = 2.10, 95% CI: 1.97-2.24) and 1995-1999 (RER = 1.82, 95% CI: 1.71-1.94) after adjusting for age and sex (p<0.0001). Further adjustment for NHL subtype reduced the relative excess risk for 1995-1999 slightly from 1.82 to 1.76 (95% CI: 1.66-1.88), but it remained statistically significantly higher than that in 2000-2004 (p<0.0001).

The number of times rituximab was dispensed for the treatment of NHL increased rapidly from 1999 (1274) to 2004 (9250) in NSW (Figure 3).

(Insert Figure 3 about here)

The trends in mortality suggested that a small rise from 1990 to 1996 (APC = 0.8, p=0.44) was followed by a substantial but non-significant fall (APC = -2.1, p=0.41) from 1996 to 2000 and then a further sharp fall from 2000 to 2004 (APC = -4.7, p=0.009). There was a small but significant increase in incidence from 1990 to 2004 (APC = 0.5, p=0.02).

**Discussion**

In this population-based study, we found that a substantial improvement in survival for NHL (5-year relative survival 73% in 2000-2004 vs 59% in 1995-1999) coincided with a sharp fall in mortality after 2000. This was approximately when rituximab was approved by the Australian Therapeutic Goods Administration for clinical use in Australia for the two commonest NHL subtypes, namely low grade or follicular lymphoma (June 1998) [3] and
diffuse large B-cell lymphomas (February 2002) [4]. These results are consistent with the beneficial effects of rituximab on cancer survival observed in clinical trials [21-23].

The findings of this population-based study are important because it includes all patients with NHL, many of whom would not have met the trials’ inclusion criteria, in a well-defined geographical area, thus reflecting the experience of real world everyday clinical practice. The main strength of the study was that we grouped subtypes of lymphomas into treatment-based categories classified according to WHO guidelines. This grouping has been used by others [24], is clinically useful [25, 26] and reduces the probability of misclassification bias [26]. Another strength is that we studied the trends in the incidence of, survival for and mortality from NHL simultaneously, and interpreted the survival trend in the context of incidence and mortality trends, as recommended by several authors [27-29].

What may explain the better survival observed in the most recent period in this study? Several factors may have contributed to the improved survival in 2000-2004. First, high-dose chemotherapy with shorter intervals between treatment cycles [30], together with better supportive care including antibiotics and growth factor to manage myelotoxicity [31], was introduced during the study period. An Australian study has also demonstrated that growth factor can be used safely and efficaciously to support intensified chemotherapy (CHOP-14) in Australian NHL patients [32]. However it only became available in 2003 and it was dispensed 1560 times in NSW in 2004 [6] so is unlikely to explain the improved survival in 2000-2004. Second, more NHL patients in NSW may have participated in clinical trials [33] which may in part have led to improved survival in the later period. Third, the introduction of highly active antiretroviral therapy (HAART) in Australia around 1997 [34] may explain in part the improved survival in 2000-2004 [35]. The use of HAART has led to both decreases in AIDS-
related lymphomas [34] and a significant improvement in prognosis [35]. Our data support this by showing a substantial increase in incidence from 1990 to 1995 (APC = 9.9, p=0.07) followed by a significant drop in incidence from 1995 to 2002 (APC = -9.0, p=0.02) among 15-44 year old male patients with B-cell aggressive NHL, the majority of whom would be affected by HIV (data not shown). The substantial (although not significant) decline (-2.1% per year) in mortality from 1996 to 2000 in our data provides further evidence for this. Fourth, changes in case-mix over time may have accounted for some of the survival benefits observed in 2000-2004. As a result of the evolution of the classification of NHL in recent decades, it was not possible to map some cases from the earlier time periods to categories comparable to those in the later period. However our use of four broad categories should reduce this problem to a minimum [26]. As shown in Table 2 the case-mix in different time periods was generally comparable except for “Other NHL”.

Finally, increasing survival over time may reflect improvements in earlier detection by screening programs. However, there is no evidence of an increase in screening to detect NHL patients earlier in Australia, as seen for breast cancer or prostate cancer. Indeed, a small and gradual increase in incidence was seen from 1990 to 2004, not a sudden substantial increase in the 2000-2004 period. Therefore, the coincidental sharp fall in mortality from 2000 to 2004 indicates that these improvements in outcomes were due to effective therapy [28, 29, 36]. Indeed, the therapeutic monoclonal antibody, rituximab, was introduced into clinical use in Australia initially for patients with relapsed or refractory indolent B-cell NHL (follicular or small lymphocytic subtypes) in 1998, and then for patients with diffuse large B-cell lymphoma (the commonest type of aggressive NHL) in early 2002. The use of rituximab for treating B-cell NHL has been wide spread in Australia (Figure 3) as universal health coverage is available and, consistent with findings from clinical trials, the improved survival was
mainly seen in B-cell lymphomas and was of a similar magnitude to that reported in the trials [21, 37]. Taking all this evidence together, we are reasonably confident that the introduction of rituximab is a major contributor to the improved survival observed in 2000-2004.

The improved survival in 2000-2004 we observed was comparable to that of a population-based study in Canada [38]. In a retrospective analysis, Sehn et al demonstrated that two-year overall survival increased for adults with DLBCL in British Columbia from 52% with CHOP to 78% after the introduction of rituximab [38]. The magnitude of the survival improvement that we observed was more modest with 2-year relative survival for aggressive NHL (>85% being DLBCL) being 75% in 2000-2004 vs 55% in 1995-1999. One of the possible reasons for this difference may be that they excluded patients with poor prognosis such as those who were HIV positive and those who did not receive curative treatment whereas our study included all patients with aggressive NHL.

Age at diagnosis was inversely associated with survival (Figure 2) which is probably due to more co-morbidities and adverse effects of chemotherapy in older patients. However, the extent of the increase in 5-year relative survival from 1995-1999 to 2000-2004 was similar in terms of an absolute percentage change, ranging from 12.8% to 16.7% for both older and younger patients (Figure 2). This is consistent with evidence from clinical trials: survival increased for both older (60-80 years) [21] and younger (18-60 years) patients [33] after the addition of rituximab to standard chemotherapy for aggressive B-cell lymphomas, the commonest NHL subtype.

The data used in this study have some limitations. The cancer registry does not collect detailed treatment information and so the data do not allow us to directly conclude that the
survival benefit observed over time was due to the use of rituximab in the treatment of NHL, although the Pharmaceutical Benefits claims data (Figure 3) provided indirect support for the observed improved survival in 2000-2004. However, these data do not allow us to estimate the fraction of patients diagnosed in 2000-2004 who actually used rituximab, thus the possibility that some unmeasured factors mentioned earlier might also have contributed to this improved survival cannot be ruled out completely. Another limitation was that the cancer registry does not collect information on patients’ comorbidities and disease extent for NHL. These factors are related to the prognosis for NHL [39]. However, our use of relative survival to account for competing mortality addressed these factors at least in part.

Conclusions

The observed rise in survival together with a fall in mortality from 2000 and a rapid increase in the use of rituximab, suggests that the benefit of adding rituximab to the standard treatment of NHL may have been experienced at least in part by this Australian NHL patient population. There are good grounds for believing that further improvement in survival, especially for patients with aggressive B-cell lymphomas, will almost certainly continue to increase as more follow-up time accrues.

Competing interests

None declared.

Authors’ contributions

XQY designed the study, obtained the cancer registry data, provided oversight of the data analyses, and drafted the manuscript. WHC participated in the design of the study, performed
the data analyses, and helped to draft the Methods and Results sections. DLO participated in
the study design, obtained the prescription data, and revised the manuscript critically. All
authors read and approved the final version of the manuscript.

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References


**Figures**

Figure 1 Relative survival by period of diagnosis for NHL, NSW Australia, 1990-2004

Figure 2 Trends in five-year relative survival for NHL by age group at diagnosis, and histological subtype, NSW Australia, 1990-2004

Figure 3 Number of times rituximab was dispensed for treatment of NHL, NSW Australia, 1999-2004
### Table 1: Number of cases by subtype of non-Hodgkin lymphoma with groups according to the WHO classification, 1990-2004 NSW, Australia

<table>
<thead>
<tr>
<th>Subtypes and groups</th>
<th>ICD-O-3 codes</th>
<th>No. of cases</th>
</tr>
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<tbody>
<tr>
<td><strong>Aggressive B-cell lymphomas</strong></td>
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<tr>
<td>Follicular lymphoma, grade 3</td>
<td>9698</td>
<td>179</td>
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<tr>
<td>Malignant lymphomas (ML), mixed small &amp; large cell, diffuse</td>
<td>9675</td>
<td>466</td>
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<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>9678-9680, 9684</td>
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<td>Burkitt's lymphoma</td>
<td>9687, 9826</td>
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<td>Lymphoblastic lymphoma</td>
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<td><strong>Indolent B-cell lymphomas</strong></td>
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<tr>
<td>Follicular lymphomas (grade 1 and 2)</td>
<td>9690-9691, 9695</td>
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<td>Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)</td>
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<td>Small lymphocytic lymphoma, Chronic lymphocytic leukemia</td>
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<td>Hairy cell leukemia</td>
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<td>Lymphoplasmacytic lymphomas</td>
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<td><strong>Other NHL</strong></td>
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<td>Mature T-cell lymphomas: peripheral, angioimmunoblastic, hepatosplenic gamma/delta T-cell</td>
<td>9702, 9705, 9708, 9714, 9716, 9827</td>
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<td>Cutaneous T-cell</td>
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<td>Mycosis fungoides and mantle cell</td>
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Table 2: Characteristics of patients with non-Hodgkin lymphoma, NSW Australia, 1990-2004

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<tr>
<th></th>
<th>Number of cases</th>
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<th>1995-1999 (n=6231)</th>
<th>2000-2004 (n=7113)</th>
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<td>Males</td>
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<td>Females</td>
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<td>43.7</td>
<td>44.8</td>
<td>44.3</td>
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<td><strong>Age at diagnosis</strong></td>
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<tr>
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<td>45-59 years</td>
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<td>60-74 years</td>
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<td>75+ years</td>
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<td><strong>NHL groupings</strong></td>
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<td>NHL NOS</td>
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