International Prognostic Index for Aggressive Non-Hodgkin’s Lymphoma Is Valid for All Malignancy Grades


An International Prognostic Index (IPI) for patients with aggressive non-Hodgkin’s lymphoma (NHL) has recently been published. The IPI is based on pretreatment clinical characteristics and developed on clinical trial patients, classified as intermediate grade according to the Working Formulation (WF). We applied this IPI in a population-based registry of NHL patients. This registry does not have the restrictions that usually hold for patients in clinical trials, eg, with respect to age and performance status. Moreover, it covers all the three WF classes (low, intermediate, and high). The IPI turned out to be of prognostic value for response rate and survival in our unselected cohort of 744 patients, as well. In each of the three WF classes separately, the four IPI classes showed going from low to high substantially decreasing response rates and survival percentages. For our cohort of WF intermediate grade patients 5-year survival levels were lower in all four IPI classes (59%, 34%, 14%, and 10%, respectively), probably reflecting the selection of clinical trial patients in the original study (73%, 51%, 43%, and 26%).

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MATERIALS AND METHODS

Patients and treatment. Included in the database were all patients (n = 1,168) newly diagnosed as and treated for NHL in the period 1981 to 1989 in one of the hospitals in the region of the CCCW, which has 1.6 million inhabitants. A first description of the database has been given by Otter et al. To be included, the patient’s diagnosis had to be confirmed by a panel of pathologists and the patient had to live inside the region of the CCCW (identified by postal code). Excluded were patients with primary cutaneous T-cell lymphoma, acute lymphoblastic and classical chronic lymphocytic leukemia, multiple myeloma, plasmacytoma, patients with only cytologic diagnosis, and patients with only a postmortem diagnosis. Anamnestic, diagnostic, and therapeutic data were retrieved from the patient’s hospital files. The follow-up for the database is annually updated for the patients alive. Treatment was left to the discretion of the local physician. The Appendix lists all participating hospitals.

Table 1. Patient Characteristics of the Total Project Group Cohort and 744 Patients from the CCCW Database

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intermediate WF (n = 3,276)*</th>
<th>Low (n = 229)</th>
<th>Intermediate (n = 426)</th>
<th>High (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>59</td>
<td>43</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>&gt;60</td>
<td>41</td>
<td>57</td>
<td>66</td>
<td>39</td>
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<tr>
<td>Karnofsky index</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=80</td>
<td>76</td>
<td>82</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>≤70</td>
<td>24</td>
<td>18</td>
<td>24</td>
<td>25</td>
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<td>Ann Arbor stage</td>
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<td></td>
</tr>
<tr>
<td>I + II</td>
<td>35</td>
<td>20</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>III + IV</td>
<td>66</td>
<td>80</td>
<td>57</td>
<td>54</td>
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<tr>
<td>Extra nodal sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=1</td>
<td>70</td>
<td>80</td>
<td>76</td>
<td>78</td>
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<tr>
<td>=2</td>
<td>30</td>
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<td>22</td>
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<td>LDH scores</td>
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<tr>
<td>≤1 × N</td>
<td>48</td>
<td>74</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>&gt;1 × N</td>
<td>52</td>
<td>26</td>
<td>49</td>
<td>67</td>
</tr>
</tbody>
</table>

Values are percentages.

* The IPI Project Group report did not provide these patient characteristics for the 2,031 patients actually used for the development of the IPI, but only for the 3,276 patients who had been entered onto the trials.

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Parameters evaluated, response, and analysis. For the present report, attention was restricted to classification according to the WF and the variables included in the IPI (age, performance status, stage, extranodal involvement, and LDH). This information was completely available for 744 patients (64%). The IPI ranges from 0 to 5 and is defined as the sum of the presence of the following five factors: age > 60 years, Karnofsky score ≤ 70, Ann Arbor stage III or IV, extranodal involvement of more than one site, and abnormal LDH level. Index values of 0 and 1 are classified as low (L), 2 as low/intermediate (L/I), 3 as intermediate/high (I/H), and 4 together with 5 as high (H).

Complete clinical staging included clinical history, physical examination, blood hematology and chemistry, chest x-ray, CT scanning or ultrasound of the abdomen or lymphangiogram supplemented by isotope liver and spleen scan, bone marrow aspirate and biopsy, and biopsy from involved tissue. Staging was qualified as incomplete (not necessarily inadequate) when information was lacking on important lymph nodes, bone marrow, or Waldeyer’s ring. For the present report, patients with an incomplete determined stage I or II were excluded because they could move to stage IV and, consequently, to an IPI one class higher as a result of a complete staging. Localizations in the tonsils, Waldeyer’s ring, and spleen were classified as nodal sites.

The following outcome parameters were studied and broken down according to the WF related to the IPI classes: complete response to therapy, overall survival from diagnosis, and for the complete responders, the relapse-free survival from end of therapy. Survival curves were calculated according to the Kaplan and Meier method; survival analysis was performed using the log-rank test.

RESULTS

The characteristics of the 744 patients of the CCCW database, reported in this report, as well as the patients used by the IPI Project Group are given in Table 1. Our intermediate grade WF patients were significantly older and had less frequent high Ann Arbor stages. The frequency of two or more extranodal sites was rather similar. Karnofsky index and LDH scores were similar.

The resulting distribution over the IPI classes can be found in Table 2. For the intermediate grade, it was comparable to the distribution in the IPI Project Group cohort. The distribution was rather similar for the high-grade NHL and shifted to the low/intermediate for the low-grade NHL.

Moreover, Table 2 gives the outcome results for complete response rates, relapse-free survival, and overall survival for each of the four IPI classes. The overall survival curves for the CCCW database (Fig 1) show that for all three WF categories the four IPI classes have a strong prognostic value. This conclusion is further supported by the complete response rates given in Table 2. The 5-year percentages for relapse-free survival, also given in Table 2, are in line with this conclusion for the intermediate grade, but not well evaluable for the low and high grades.

Comparison of our WF category intermediate grade with the results of the IPI Project Group showed some remarkable differences. As documented in Table 2, complete response rates, relapse-free survival at 5 years, and overall survival at 5 years are substantially higher for the IPI Project Group patients.

DISCUSSION

The members of the IPI Project Group developed a prognostic index (IPI) for patients with aggressive non-Hodgkin’s lymphoma. They focused on the prognostic value of pretreatment clinical characteristics. In total, 3,276 adult patients, originally included in several clinical trials, entered their
OVERALL SURVIVAL

Fig 1. Survival among 744 patients in Working Formulation low, intermediate, and high according to risk groups defined by the International Prognostic Index. L denotes low risk, L/I low/intermediate risk, I/H intermediate/high risk, and H high risk. Values for these groups are also shown in Table 2.

study; for 2,031 patients (62%), information on the clinical characteristics was complete. Development of the index was done on a training sample of 1,385 patients and validation on the remaining 646 patients.

Our intention was to study whether the prognostic value of the IPI could be confirmed on a different patient cohort and to see whether the usefulness of the IPI could be extended to NHL patients of other malignancy grades. The differences between the IPI Project Group’s NHL population and ours have to be emphasized. Their population was intermediate grade WF, whereas ours covered the three distinct grades low, intermediate, and high. Their population had to fulfill the inclusion criteria of phase II and phase III clinical trials. Our population included all patients diagnosed as and treated for NHL in a given region, which is especially reflected by a markedly older cohort. Their population had a protocolized combination chemotherapy treatment, all regimens containing doxorubicin. In our study cohort, treatment was left to the discretion of the physician. Thus, compared with the IPI Project Group cohort our intermediate grade study population is more heterogenous, but represents the average presenting population of NHL patients. This probably explains why the outcome in our intermediate grade is worse compared with the IPI Project Group outcome (Table 2). However, the prognostic value of the IPI is confirmed in our series of intermediate grade patients. Moreover, the prognostic value of the IPI turned out to hold also for the low-grade and high-grade NHL in our series (see Fig 1), so extension to these categories is justified for the patients in our database.

López-Guillermo et al. studied the IPI for a single institution series of 125 low-grade lymphomas. They found good prognostic power for the IPI in their series, also when restricted to 107 follicular lymphomas. They reported a similar tendency for the L/I and I/H risk classes and decided to classify the patients in only three index classes (low, intermediate, and high). We did not find a similar tendency.

Contrary, Avilés reported recently for a single institution series of 238 low-grade NHL patients no prognostic value for the IPI. For his series with a short median follow-up (treatment period 1986 to 1991) and uniformly treated with combined chemotherapy followed by radiotherapy to sites of nodal involvement, complete response rates, as well as 7-year survival percentages, were very similar.

We conclude that the International Prognostic Index, divided into four categories, is applicable to unselected NHL patients for all three malignancy grades of the WF.

APPENDIX

Participating Hospitals and Cooperating Physicians:
Academisch Ziekenhuis, Leiden (Ph.M. Kluin, J.C. Kluin-Nelemans, J.H.J.M. van Krieken, J.W.H. Leer, E.M. Noordijk, A. Snijders-Keilholz); Antoniushove, Leidschendam (M.G. Herben); Bronovo, The Hague (R. Bieger, M. Voortman); Diaconessenhuis, Leiden (M.C.B. Gorsira, H. van Slooten); Diaconessenhuis, Voorburg (J.R. van der Mey); Groene Hart Ziekenhuis (localization Bleuland), Gouda (K.J. Heering, J.B. Rahder); Groene Hart Ziekenhuis (localization Jozef), Gouda (R.F.A. Simonis, A.M.E. van der Torren-

REFERENCES


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