The challenge of p53 as prognostic and predictive factor in Hodgkin’s or non-Hodgkin’s lymphoma

Abstract The results of individual studies examining the role of p53 as a predictive and prognostic factor in lymphoid malignancies have varied considerably. In order to summarize the available data on the overexpression or mutation of p53 in Hodgkin’s and non-Hodgkin’s lymphoma, a systematic literature review was performed. Twenty-four studies met the eligibility criteria. With respect to non-Hodgkin’s lymphoma, most studies seem to support the hypothesis that patients whose tumors contain wild-type p53 respond better to treatment and have increased survival rates. If true, the implication may be that patients with p53 mutated tumors could be selected for non-standard treatment. With respect to Hodgkin’s lymphoma, comparable associations were rarely reported. However, techniques for assessing the inactivation of p53 varied widely. Furthermore, in most instances, the study design and/or statistical methods did not allow sufficient analyses of the influence of confounding factors such as histologic type, stage, first-line and salvage treatment, etc. Therefore, it remains unclear whether the apparent influence of p53 status on outcome in non-Hodgkin’s lymphoma is independent of established parameters such as stage, performance status, etc. Further studies involving large numbers of specimens derived from patients treated in clinical trials with identical regimens, follow-up and salvage strategies are needed. These studies should also be stratified according to histologic subtypes.

Keywords Lymphoma · Non-Hodgkin’s lymphoma · Hodgkin’s lymphoma · Prognostic factors · p53

Introduction

Most Hodgkin’s lymphoma and a considerable proportion of non-Hodgkin’s lymphoma initially respond to radiotherapy and several chemotherapy regimens, all of which activate an endogenous biochemical pathway for cell suicide, known as apoptosis [29]. Depending on histologic type and stage of disease, the use of radiotherapy and chemotherapy, either alone or in combination, will eventually cure certain subgroups of patients. However, even within well-defined subgroups, response to treatment cannot be expected to be uniform. Of course, it would be desirable to know in advance whether an individual patient will respond to a specific therapy so that the optimal therapy could be chosen for each patient. For many years, researchers have tried to identify factors that would be useful in predicting the response to treatment and prognosis. In recent years, there has been increasing interest in genetic abnormalities and biologic factors such as the tumor suppressor gene p53 [19, 26].

At the most basic level, p53 is a nuclear phosphoprotein that functions as a transcription factor, i.e. as a modulator which can turn crucial genes either on or off [29, 33]. It also inhibits DNA replication and is a checkpoint control molecule for progression of the cell cycle from G1 to S-phase and also from G2 to M [20, 33]. It is through these general mechanisms that wild-type p53 slows proliferation down. Furthermore, p53 is also involved in the regulation of apoptosis, although p53-independent pathways have been identified [1]. By blocking angiogenesis, p53 may influence even more factors crucial for tumor development and progression [12]. Inactivation of p53, for example, by mutation, loss, se-
Results

The p53 status and its role as a prognostic factor for survival in Hodgkin’s lymphoma

As summarized in Table 1, four studies evaluated patients with Hodgkin’s lymphoma. All of them used immunohistochemistry (IHC) and positive p53 staining of Reed-Sternberg/Hodgkin’s cells were detected in the majority of cases (65% or more, depending on antibody and cutoff value) [2, 23, 32, 35]. None of these studies included a separate analysis of lymphocyte predominant vs classic Hodgkin’s lymphoma. Some authors described a relation between positive IHC for p53 and both advanced stage of disease and histology [32], whereas others found no significant correlation [35]. Three of these studies provided no indication that p53 positive cases have a shorter survival rate [2, 23, 35]. The other suggested that patients whose tumors show a positive staining for p53 in more than 25% of the cell nuclei have a shorter overall survival rate [32]. However, it was this study that found a significant correlation.

Table 1 Summary of study data (Hodgkin’s lymphoma). Multivariate analysis was considered questionable if it was not stated what factors were included. HD Hodgkin’s disease, RT radiotherapy, CHT chemotherapy, IHC immunohistochemistry, Ab antibody, n.a. not available

<table>
<thead>
<tr>
<th>Reference</th>
<th>Histology</th>
<th>Stage</th>
<th>Treatment</th>
<th>IHC</th>
<th>DNA-based technique</th>
<th>5-year survival rates</th>
<th>Multivariate results for p53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smolewski et al. [32]</td>
<td>All types of HD</td>
<td>All</td>
<td>RT, CHT, or both n.a.</td>
<td>Ab DO-7, 65% positive(^a)</td>
<td>n.a.</td>
<td>+56% –100%</td>
<td>Significant, but questionable</td>
</tr>
<tr>
<td>Brink et al. [2]</td>
<td>Nodular sclerosis and mixed type(^b)</td>
<td>All</td>
<td>n.a.</td>
<td>Ab DO-7, 67% positive(^a)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Not significant</td>
</tr>
<tr>
<td>Morente et al. [23]</td>
<td>All types of HD(^c)</td>
<td>All</td>
<td>RT, CHT, or both n.a.</td>
<td>Ab CMI, 93% positive(^f)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a., univariate not significant</td>
</tr>
<tr>
<td>Xerri et al. [35]</td>
<td>All types except lymphocyte-depl.</td>
<td>All</td>
<td>n.a.</td>
<td>Ab DO-1 &amp; 1801, 75 and 40% positive(^f)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a., univariate not significant</td>
</tr>
</tbody>
</table>

\(^a\) Estimated from survival curves if not given in detail (+ means positive IHC, – means negative IHC).
\(^b\) Multicenter study without central histology review
\(^c\) Multicenter study with central histology review

\(^d\) Staining in ≥1% of cells
\(^e\) Staining in ≥10% of cells
\(^f\) Any staining