ERCC1 Expression in Diffuse Large B-Cell Lymphoma Patients Treated with a Cisplatin-Based Regimen: A Brief Communication

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ABSTRACT

There is growing interest in defining biomarkers that could predict response to different chemotherapeutic agents. Excision repair cross complement 1 (ERCC1) enzyme has been shown to predict benefit of cisplatin in different types of cancer. As cisplatin-based regimens are frequently used in the salvage treatment of diffuse large B-cell lymphomas (DLBCL), we thought of conducting a small pilot study to determine whether ERCC1 is expressed in this disease or not. Out of seven patients examined, only one had a 25% ERCC1 expression, which could represent a tumour truly expressing this marker. However, expression was not able to predict response to treatment. It remains unclear whether ERCC1 could serve as a predictive marker for cisplatin in this disease requiring further studies.

Key Words: ERCC1 – Large B-cell lymphoma – Cisplatin resistance.

INTRODUCTION

Cisplatin is an alkylation agent which is frequently used in cancer treatment. Cisplatin binds to DNA creating a platinum-DNA and interstrand adducts, thereby inhibiting DNA replication. Excision repair cross complement 1 (ERCC1) enzyme plays a rate-limiting role in recognizing and removing DNA adducts induced by cisplatin [1]. ERCC1 belongs to the nucleotide excision repair (NER) pathway and its high expression has been shown to be associated with cisplatin resistance [2]. In non-small cell lung cancer patients receiving cisplatin-based chemotherapy, negative ERCC1 expression has been shown to predict response and improved survival in both early [3] and advanced [4] settings. Similar results were shown in patients with head and neck squamous cell carcinoma [5]. As cisplatin-based regimens are frequently used in treating patients with relapsing diffuse large B-cell lymphoma (DLBCL), we thought of conducting a small pilot study to determine whether ERCC1 is expressed in this disease or not.

MATERIAL AND METHODS

We searched our data-base for DLBCL patients diagnosed and treated with a cisplatin-based regimen at the European Institute of Oncology, Milan for whom a paraffin block was available for pathological and immunohistochemical assessment.

Immunohistochemistry for ERCC1 was performed on 3 μm-thick sections using the monoclonal antibody 8F1 (Neomarkers, Freemont, CA, working dilution 1:150) with an automated immunostainer (Benchmark XT, Ventana Medical Systems, USA). We used the commercially-available detection kit (Dako EnVision Plus-HRP, Dako, USA), according to the manufacturer’s instructions. Heat-induced antigen retrieval was performed by placing the slides in citrate buffer for 30 minutes in a thermostatic water-bath at 99°C. All the immunohistochemical reactions were evaluated semi-quantitatively and results expressed as the percentage of tumour cells showing definite nuclear immunoreactivity in the neoplastic population.

RESULTS

Seven patients (6 males and 1 female) with a median age of 45 years were randomly selected for this pilot study and the pathologist was blinded as regards their treatment outcome. All patients were treated with the ESHAP (etoposide, methyl prednisolone, high dose ara-c and
cisplatin) regimen in the second line setting. Immuno-histochemical assessment for ERCC1 showed an expression of 0% in three patients, 2%, 3%, 15% and 25% in one patient. Table (1) summarizes the results of our series.

Table (1): Results.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Chemotherapy regimen</th>
<th>Treatment setting</th>
<th>Response to treatment</th>
<th>ERCC1</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>71 M</td>
<td>ESHAP</td>
<td>2nd line</td>
<td>Yes</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>41 M</td>
<td>ESHAP</td>
<td>2nd line</td>
<td>Yes</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>23 F</td>
<td>ESHAP</td>
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<td>Yes</td>
<td>3%</td>
</tr>
<tr>
<td>4</td>
<td>37 M</td>
<td>ESHAP</td>
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<td>Yes</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>55 M</td>
<td>ESHAP</td>
<td>2nd line</td>
<td>No</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>55 M</td>
<td>ESHAP</td>
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<td>No</td>
<td>0%</td>
</tr>
<tr>
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<td>32 M</td>
<td>ESHAP</td>
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<td>Yes</td>
<td>2%</td>
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</table>


DISCUSSION

Little controversy exists as regards the cut-off value for a truly positive ERCC1 expression. Previous reports have shown that an expression of 25% or higher is considered positive [4], while others considered a cut-off value of 50% [3]. In our series, only one patient (patient #1) had an expression of 25% (Fig. 1). Despite the high ERCC1 expression, this patient responded well to the cisplatin based-chemotherapy, which argues against the proposed hypothesis. A possible explanation for this paradox would be the chemo-sensitivity of lymphoma to agents in the ESHAP regimen other than cisplatin. In the treatment of relapsed DLBCL, salvage chemotherapy is often used before autologous stem cell transplant [6] to test for chemo-sensitivity and to decrease tumour load. Even if there is no standard salvage regimen, a cisplatin-based combination is frequently used. Recently other agents have shown comparable results with lower adverse events like gemcitabine and vinorelbine [7]. Whether ERCC1 could serve as a predictive marker for the use of cisplatin in this setting or not remains an open question.

To our knowledge, this is the first report on ERCC1 expression in DLBCL. One patient had an immuno-reactivity in 25% of the neoplastic cells, thus possibly representing tumours truly over-expressing ERCC1. However, the limited number does not enable us to draw solid conclusions. Further evaluation is required to define whether ERCC1 expression in DLBCL could have any clinical implications.

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REFERENCES


Fig. (1): 25% expression of ERCC1 in DLBCL.