Lenalidomide treatment in relapsed/refractory B-cell lymphomas: A single center real-life experience

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Abstract

As an immunomodulatory drug, lenalidomide has been shown to have anti-lymphoma activity and is used in combination with several agents in the treatment of patients with relapsed/refractory disease. In this study, we aimed to evaluate the efficiency of lenalidomide in the treatment of B-cell NHL. This retrospective study included patients with relapsed/refractory B-cell NHL who received lenalidomide treatment between March 2018 and January 2021. Patients’ demographic data, dose, and duration of the lenalidomide treatment, combined agents, response rates, side effects, and survival rates were evaluated. Twelve patients who diagnosed with relapsed/refractory NHL were included in the study. Lenalidomide treatment was initiated in combination with rituximab for nine of these patients and with temozolomide for the remaining three of them. At the initiation of the lenalidomide treatment, patients’ median age was 72.5 (24-83) years. Number of females/males was 9/3. Nine of the patients were diagnosed with diffuse large b-cell lymphoma (DLBCL), 3 of whom had isolated central nervous system lymphoma (CNS) and 1 had Richter transformation of chronic lymphocytic leukemia. Two patients were diagnosed with mantle cell lymphoma (MCL) and 1 patient was diagnosed with marginal zone lymphoma. The median treatment duration was 4 (1-20) months. In the response assessment, 4 patients had complete response while progressed disease was observed in 5 patients. Three patients died before response assessment. In the median 33-month follow-up, progression-free survival and total survival were found as 4 (1-20) and 7 (1-22) months respectively. Due to its low toxicity profile and activity, lenalidomide could be a good option especially for elderly and fragile B-cell lymphoma patients. It is an agent to be considered particularly in lymphomas with CNS involvement with its good CNS penetration. Its synergistic effect may give better results when used in combination with several anti-lymphoma drugs.

Keywords: B-cell lymphoma, lenalidomide, immunomodulatory drug, relapsed/refractory disease

Introduction

Non-Hodgkin lymphomas (NHL) are a heterogenous group of diseases and nearly 85% of them is composed of B-cell lymphomas. They are mainly divided in two groups as aggressive lymphomas and indolent lymphomas [1]. Rituximab, a human anti-CD20 monoclonal antibody, is frequently used in combination with chemotherapy for the treatment of B-cell lymphomas. Although cure is usually possible in aggressive lymphomas with these treatments, the effectiveness of the treatment is limited due to toxicity and recurrence is observed in many of the patients. Thus, there is a need for alternative ways of treatment for such patients [2]. Indolent lymphomas, on the other hand, respond very well to the initial treatment, but eventually relapse [3]. Several treatment strategies could be used at the relapse of both aggressive and indolent lymphomas. While planning the treatment of these patients, response to previous treatment, response durations age and performance at relapse and the patient’s preferences must be considered. Most of the patients are not suitable for high-dose chemotherapy and stem-cell transplantation due to advanced age, low performance, and comorbidities. Recently, new treatment options with low-toxicity profile are available for such patients [4]. Lenalidomide is an immunomodulatory drug (IMID), which binds to the cereblon E3 ubiquitin ligase complex and leads to the ubiquitination of the transcription factors Aiolos and Ikaros. It exerts its anti-lymphoma effects with its antiangiogenic, immunomodulatory and direct cytotoxic properties [5,6]. Vascular endothelial growth factor (VEGF) and its receptors are essential for the formation of blood vessels in carcinogenesis [7]. Lenalidomide shows its antiangiogenic effects via the upregulation of both VEGF and IL-6 [8]. Lenalidomide has several immunomodulatory effects. It improves T-cell activity as well as increasing both the number and activation of NK cells [9]. Immunologic synapse formation of tumor infiltrating T-cells is impaired in lymphomas and it was demonstrated that this defect was repaired with lenalidomide [10].
Also, lenalidomide enhances monocyte-mediated and natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) via enhancing Fc-gamma receptor signalling and increases the efficacy of rituximab [11]. Lenalidomide shows its direct anti-tumor effects by causing cell cycle arrest and inducing apoptosis in tumor cells [12,13]. Due to these different mechanisms of action and synergistic effects, its clinical efficacy has been demonstrated both in the first-line treatment of many lymphoma subtypes and in the treatment of relapse/refractory disease [3].

In the present study, we aimed to evaluate the efficacy and toleration of lenalidomide in our patients with relapsed or refractory B-cell lymphoma.

Materials and Methods

Patients

Patients who received lenalidomide in combination with several agents due to relapsed or refractory B-cell lymphoma between March 2018 and January 2021 were included in the present retrospective study. Four patients were not suitable for conventional chemotherapy and 8 patients were used the other treatment options.

Approval was obtained from the ethics committee of our institute for this research study. Information concerning the patients’ demographic data, diagnosis types, stages at diagnosis, number of treatments received prior to lenalidomide, agents used combination with lenalidomide, lenalidomide-related haematological and non-haematological side-effects, response and survival states was obtained from patients’ records.

Table 1. Patients’ demographic and clinical features at the time of lenalidomide therapy.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Stage</th>
<th>Gender</th>
<th>Bulky disease</th>
<th>Previous treatments</th>
<th>Lenalidomide based regimen</th>
<th>Adverse events</th>
<th>Response</th>
<th>Duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>DLBCL</td>
<td>78</td>
<td>3BS</td>
<td>Female</td>
<td>-</td>
<td>Rituximab plus Bendamustine</td>
<td>Rituximab plus lenalidomide</td>
<td>Neutropenia, emesis</td>
<td>Response</td>
<td>7</td>
</tr>
<tr>
<td>Patient 2</td>
<td>DLBCL</td>
<td>82</td>
<td>4B</td>
<td>Male</td>
<td>-</td>
<td>Rituximab plus Bendamustine</td>
<td>Rituximab plus lenalidomide</td>
<td>-</td>
<td>CR</td>
<td>1</td>
</tr>
<tr>
<td>Patient 3</td>
<td>DLBCL</td>
<td>72</td>
<td>3B</td>
<td>Female</td>
<td>-</td>
<td>R-CHOP</td>
<td>Rituximab plus lenalidomide</td>
<td>-</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Patient 4</td>
<td>DLBCL</td>
<td>24</td>
<td>4B</td>
<td>Female</td>
<td>+</td>
<td>R-CHOP, MATRIX, Cyber Knife</td>
<td>Rituximab plus lenalidomide</td>
<td>-</td>
<td>CR</td>
<td>7</td>
</tr>
<tr>
<td>Patient 5</td>
<td>DLBCL</td>
<td>83</td>
<td>4A</td>
<td>Female</td>
<td>+</td>
<td>R-CHOP, R-GDP</td>
<td>Rituximab plus lenalidomide</td>
<td>Neutropenia, emesis</td>
<td>CR</td>
<td>1</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Primary CNS Lymphoma</td>
<td>34</td>
<td>1E</td>
<td>Male</td>
<td>-</td>
<td>R-MPV</td>
<td>Lenalidomide plus temozolomide</td>
<td>-</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Primary CNS Lymphoma</td>
<td>68</td>
<td>1E</td>
<td>Female</td>
<td>-</td>
<td>Rituximab plus methotrexate plus cytarabine, Ibrutinib</td>
<td>Lenalidomide plus temozolomide</td>
<td>-</td>
<td>Progression</td>
<td>1</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Primary CNS Lymphoma</td>
<td>49</td>
<td>1E</td>
<td>Female</td>
<td>-</td>
<td>R-MPV, Autologous transplantation, Ibrutinib</td>
<td>Lenalidomide plus temozolomide</td>
<td>-</td>
<td>NA</td>
<td>2</td>
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<tr>
<td>Patient 9</td>
<td>Richter from CLL</td>
<td>63</td>
<td>4B</td>
<td>Female</td>
<td>+</td>
<td>R-CHOP, R-FC, R-DHAP</td>
<td>Rituximab plus lenalidomide</td>
<td>Neutropenia, emesis</td>
<td>Progression</td>
<td>15</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Mantle Cell Lymphoma</td>
<td>73</td>
<td>3SB</td>
<td>Male</td>
<td>-</td>
<td>R-CHOP, BORID, Ibrutinib</td>
<td>Rituximab plus lenalidomide</td>
<td>Neutropenia, emesis</td>
<td>CR</td>
<td>2</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Mantle Cell Lymphoma</td>
<td>80</td>
<td>3B</td>
<td>Female</td>
<td>-</td>
<td>R-CHOP, R-CHOP</td>
<td>Rituximab plus lenalidomide</td>
<td>-</td>
<td>Progression</td>
<td>4</td>
</tr>
<tr>
<td>Patient 12</td>
<td>Nodular Marginal Zone Lymphoma</td>
<td>82</td>
<td>4B</td>
<td>Female</td>
<td>-</td>
<td>Rituximab plus Bendamustine, R-CVP</td>
<td>Rituximab plus lenalidomide</td>
<td>-</td>
<td>Progression</td>
<td>4</td>
</tr>
</tbody>
</table>


Treatment

Rituximab (intravenous) and lenalidomide (oral) combination were administered as follows; rituximab 375 mg/m² on days 1, 8, 15 and 22 at first cycle, on day 1 at 2nd-5th cycles, lenalidomide at dose of 25 mg daily on days 1–21 of each 28-day cycle.

Temozolomide and lenalidomide combination was given orally as lenalidomide daily on days 1–21 of each 28-day cycle at dose of 15 or 25 mg, temozolomide at dose of 50 mg/m² daily on days 1-5.

Response assessment generally was made after 3 cycles using the revised Lugano criteria [14].

Side effects were evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The dose of Lenalidomide was decreased in patients who showed side effects. All patients received antiaggregant or anticoagulant agents for thrombosis prophylaxis.

Results

In the present study, 12 patients with b-cell lymphoma who met the study criteria were evaluated. Nine of the patients received lenalidomide in combination with rituximab and three patients received lenalidomide in combination with temozolomide. The median age before lenalidomide treatment was 72.5 (24-83) years.
Nine of the patients were female and 3 were male. In terms of lymphoma subtypes, 5 patients had diffuse large B-cell lymphoma (DLBCL), 3 had primary central nervous system lymphoma, 2 had mantle cell lymphoma, 1 had Richter’s transformation of chronic lymphocytic leukemia, and 1 patient had nodal marginal zone lymphoma.

Lenalidomide was used in combination with temozolomide in 3 patients with primary central nervous system lymphoma. For all the patients, lenalidomide was initiated as second line in 4 patients, third line in 5 patients and forth line in 3 patients. Two of the patients had autologous stem cell transplantation prior to the lenalidomide treatment. Patients’ demographic data, disease characteristics, previous treatments, response to lenalidomide based treatment and adverse events were also shown in Table-1. Initial dose of lenalidomide was 15 mg/day in two patients and 25 mg/day in the other patients. The median dose of lenalidomide was 25 mg (15-25) mg. The dose reduction was performed in 3 patients due to side effects. Thrombosis prophylaxis was administered to all patients with acetylsalicylic acid in 7 patients and low molecular weight heparin in 5 patients.

The median treatment duration was 4 (1-20) months. For the responses after 3 cycles of lenalidomide treatment, 4 patients had complete response (33%) and 5 patients had progressive disease (41%). Of the patients who had complete response, relapse was observed in the 20th month in one and in the 7th month in another. Despite complete response in one patient, the treatment was discontinued after the 5th cycle due to side effects. The other patient with complete response is still under follow-up in the 10th month with lenalidomide treatment. In the median 33-month follow-up, progression-free survival (PFS) and overall survival (OS) were found as median 4 (1-20) and 7 (1-22) months respectively.

As for the adverse events, 7 patients (58%) developed neutropenia (5 patients in grade 1-2; and 2 patients in grade 3) and 2 patients (16%) developed thrombocytopenia (1 patient in grade 1 and 1 patient in grade 4). We observed nausea and vomiting in 2 patients and treatment-associated infection in 3 patients as the non-haematological side effects.

**Discussion**

Lenalidomide has been shown to have high efficacy in both the front-line and relapsed/refractory treatment of indolent lymphomas [3]. Combination of lenalidomide with rituximab increases antibody-associated cellular toxicity, immune synapse formation, monocyte-associated toxicity, and direct cytotoxicity against lymphoma cells [10,15,16]. In the treatment of relapsed/refractory B-cell lymphoma, overall response rates of 62% to 77% can be obtained through lenalidomide and rituximab combination [17,18]. In our study, only 1 patient had nodal marginal zone lymphoma as a low-grade lymphoma and this patient received lenalidomide/rituximab combination as the 3rd line treatment but was found to have been progressed after the 4-month treatment. In the phase 3 AUGMENT study, lenalidomide and rituximab combination was compared with rituximab and placebo in patients with relapsed/refractory follicular lymphoma and marginal zone lymphoma. In this study, although the addition of lenalidomide to rituximab treatment increased response rates and PFS in all groups, the OS advantage could not be shown in patients diagnosed with marginal zone lymphoma [3]. While the efficacy of lenalidomide and rituximab in the first-line treatment in marginal zone lymphoma was shown [19], further data is needed on its efficacy in the case of relapsed or refractory disease. In our study, all the patients, except for one, had aggressive lymphoma. Five of them had DLBCL and 1 had Richter’s transformation. The efficacy of lenalidomide and rituximab combination in DLBCL and transformed lymphomas was evaluated by a phase 2 study. Additionally, grade 3 follicular lymphoma patients were included in this study. The overall response rate was 33%. PFS and OS were 3.7 months and 10.7 months respectively [20]. In another study, lenalidomide and rituximab combination were evaluated in 23 patients who were aged over 65 and were diagnosed with DLBCL. The overall response rate was found as 35% in this elderly and vulnerable patient group who had previously received multiple lines of treatment [21]. In a single-centre study, 21 patients with relapsed/refractory DLBCL including seven patients with secondary CNS involvement and 3 patients with transformed follicular lymphoma who received lenalidomide plus rituximab were evaluated. The patient group in this study was like ours overall response rate was observed as 38% (21% complete response). PFS and OS were found as 1,8 months and 7.3 months respectively [22]. All these findings are compatible with the results observed in our study.

Our study included 2 mantle cell lymphoma patients. These patients received the lenalidomide and rituximab combination as the third- and fourth-line treatment, and progression was observed in the 2nd and 4th months of treatment respectively. The efficacy of the lenalidomide and rituximab combination on the first-line treatment of mantle cell lymphoma was shown in a phase 2 multicentre study. In this study conducted with a total of 38 patients, total response was 92.2%, PFS for two years was 85% and OS for two years was 97% [23]. With these successful results, lenalidomide and rituximab found a place among the standard treatments in the first-line treatment of mantle cell lymphoma. However, it is unfortunately not very possible to mention such response rates in the case of relapsed/refractory mantle cell lymphoma. In a phase 2 study that included 44 relapsed/refractory patients who had received prior 1-to-4-line of treatments, the efficacy of lenalidomide and rituximab was evaluated. The overall response rate was observed as 57% (36% complete response), PFS was 11.1 months and OS was 24.3 months [24]. Due to the small number of mantle cell lymphoma patients in our study, subgroup analysis could not be performed, but the patients relapsed within 4 months at the latest. This could have resulted from the fact that both patients were over 70 years and heavily pre-treated patients.

In this study, 3 patients received lenalidomide and temozolomide treatment due to primary central nervous system lymphoma. Among these patients, the disease control was maintained for 7 months in the HIV-positive one, while the other two progressed within 2 months at the latest. All three patients received lenalidomide in combination with temozolomide which is an alkylating agent with considerably good penetration to the central nervous system. Temozolomide is an agent whose efficacy has been shown both in the first line treatment and in relapsed/refractory disease treatment of primary CNS lymphoma [25]. Lenalidomide, on the other hand, is an immunomodulatory drug with a considerably good penetration to the central nervous system [26]. The efficacy of lenalidomide and rituximab combination in central nervous...
system lymphomas was evaluated in a multicentre phase 2 study. The study included primary intraocular lymphomas in addition to the patients diagnosed with primary central nervous system lymphoma. Of the 45 patients whose responses could be assessed, the overall response rate was observed as 35.6%, progression-free survival as 7.8 months and total survival as 17.7 months [27]. Some case series also indicate that lenalidomide can be effective as monotherapy in primary CNS lymphoma [28,29]. However, in the literature review, we could only find 1 case presentation which used lenalidomide in combination with temozolomide in the treatment of relapsed primary CNS lymphoma. In this case presentation, disease control was achieved for up to 6 months in an 83-year-old patient. In our study, similarly, a progression-free period was achieved that can be accepted as quite good for relapsed primary CNS lymphoma in one patient while 2 patients had rapid progression. These findings imply that lenalidomide and temozolomide can be an option for especially vulnerable and relapsed/refractory primary CNS lymphomas. It could be possible to obtain a more efficacious treatment by adding such agents as ibrutinib that has good central nervous system penetration. The efficacy of lenalidomide combined with rituximab and ibrutinib has been demonstrated in relapsed/refractory mantle cell lymphoma and DLBCL [30,31]. In our study, ibrutinib was not used in combination with lenalidomide in any of the patients, but it was included in the previous or following line treatments. In AUGMENT trial, neutropenia was observed in 58% of patients and it was grade 3 or 4 in 50% of patients [3]. It was observed as 58% in our study too but grade 3 or 4 neutropenia was observed in only 17% of our patients. Despite our study population had older age and more prior lines of therapy, grade 3 or 4 neutropenia was fewer. Probably, it was due to our small study population and shorter treatment duration. Thrombocytopenia was observed in 15% of patients in AUGMENT trial and similarly it was observed 16% in our study. We observed nausea and vomiting in 16% of our patients and this was similar with the AUGMENT trial. Interestingly, the infection rate in our study was lower than AUGMENT trial (25% vs 63%) despite our more fragile study population. We could not determine this situation but it can be due to smaller study population and shorter treatment duration again.

Conclusion

Our study and some others in the related literature show that lenalidomide can be used in combination with several agents for the treatment of relapsed/refractory B-cell lymphoma. The synergistic activity of lenalidomide with other anti-lymphoma agents is remarkable. It can be a good option with its low-toxicity profile and acceptable efficacy particularly for elderly and vulnerable patients.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

This study was approved by Firat University Non-invasive Clinical Research Ethics Committee (date: 22.04.2021, approval number: 2021/06-09) and conducted in accordance with the Helsinki Declaration.

References


