Lenalidomide, idelalisib, and rituximab are unacceptably toxic in patients with relapsed/refractory indolent lymphoma

Understanding of the tumor microenvironment has led to the development of novel agents for lymphoma, although few studies have combined these as a therapeutic strategy. We report unacceptable toxicity from such a biological triplet. Patients were treated in a multiarm phase 1 study using different combinations of chemotherapy, immunomodulators, and anti-CD20 monoclonal antibodies in combination with idelalisib (www.clinicaltrials.gov; #NCT01088048). We report on the cohort of patients treated with idelalisib, lenalidomide, and rituximab. The inclusion criteria were relapsed indolent lymphoma, age >18 years, measurable disease, and performance status ≤2. Patients were excluded if they had anticancer therapy within 4 weeks, prior allogeneic stem cell transplant, or active central nervous system involvement, were pregnant or breast-feeding, had active serious infection, serum creatinine ≥2.0 mg/dL, neutrophils <1.0 × 10⁹/L or platelets <75 × 10⁹/L, bilirubin ≥2 mg/dL, aspartate aminotransferase or alanine aminotransferase (ALT) ≥2 times the upper limit of normal, Child-Pugh class B or C hepatic impairment, infection with HIV or hepatitis B or C virus, or prior treatment with idelalisib.

Treatment comprised lenalidomide 5 mg (days 8-21 cycle 1, days 1-21 thereafter), rituximab 375 mg/m² day 1, and idelalisib 150 mg twice daily from day 1 (cycle 1, 35 days; subsequent cycles, 28 days). Seven patients enrolled in the initial cohort. The median age was 62 (range, 49-72) years. Five patients had follicular lymphoma (FL), 1 had small lymphocytic lymphoma, and 1 had marginal zone lymphoma. The median number of prior treatments was 1.5 (range, 1-5). None had liver disease or hepatic involvement with lymphoma. Three of the 6 patients (50%) who developed liver function test abnormalities were taking statins at study entry. The first 4 patients developed ALT elevation (2 grade 2 and 2 grade 4). Lenalidomide was held in all patients. Four patients (57%) had elevation in bilirubin (grade 1 in 2 patients, grade 2 in 1 patient, and grade 4 in 1 patient). ALT elevations of the four subjects began on days 22, 25, 30, and 36, at which point patients had 15 to 21 days of concurrent lenalidomide. All therapy was interrupted until resolution of abnormalities. No patients developed renal impairment at the time of development of liver function test abnormalities. Three remaining patients had 1 week of concurrent lenalidomide before discontinuation. These patients continued on idelalisib and rituximab, but 2 developed subsequent grade 3 (days 50 and 98) ALT elevations (Figure 1A). All patients had imaging: 2 showed diffuse hypochoicogenicity and 1 borderline fatty hepatomegaly. The median time to resolution of ALT and aspartate aminotransferase was 42 (range, 21-59) and 14 (range, 3-38) days, respectively. Four patients resumed idelalisib alone; patient 2 developed recurrent elevation in ALT on rechallenge. This arm of the study was closed to new patient enrollment. Two patients died due to toxicity and are described below.

Patient 6 (62 years, male, FL) presented on day 90 with dyspnea and chest pain with computed tomography suggestive of pneumonia. Idelalisib was discontinued, and bronchoalveolar lavage isolated Fusarium species. Although the total bilirubin increased initially after commencing voriconazole, this trend continued after therapy was switched to liposomal amphotericin B. Quantitative cytomegalovirus and repeat hepatitis testing were negative; potentially hepatotoxic drugs were discontinued.

Liver biopsy on day 112 showed acute cholangitis with mixed portal inflammation and centrilobular cholestasis without viral inclusions, fungal organisms, or lymphoma. Immune dysregulation was suspected and peripheral blood lymphocytes were analyzed on samples collected prior to therapy and day 120. Analysis of T-cell subsets revealed reduced numbers of total T cells, CD4⁺ and CD8⁺ T cells, and natural killer cells at day 120, but Foxp3⁺ regulatory T-cell numbers were unchanged (Figure 1B). Interestingly, both CD4⁺ and CD8⁺ T cells showed broad expression of markers consistent with marked activation at day 116 (Figure 1C). To abrogate immunologic dysregulation, the patient was given pulse methylprednisolone on day 120 and continued prednisone at doses of ≥30 mg/day with transient stabilization of liver function. Mycophenolate mofetil and ursodeoxycholic acid were initiated but ineffective, and the patient died of hepatic failure.

Patient 5 (68 years, female, FL) experienced grade 3 ALT elevation requiring dose interruption during cycle 2, and she achieved complete response to therapy after cycle 3. Idelalisib and rituximab were recommenced from cycle 4. She had reported no significant gastrointestinal adverse events other than grade 1 constipation. During treatment cycle 7, she developed abdominal pain, nausea, vomiting, and hematochezia. Because of suspected idelalisib-induced colitis, high-dose IV corticosteroids were administered with symptomatic improvement. However, prior to discharge, she developed suspected...
septic shock with gram-positive bacteremia, acute kidney injury, and fatal respiratory failure.

Neither doublet (lenalidomide/rituximab, idelalisib/rituximab) has been associated with serious hepatotoxicity. Grade 3 ALT elevation was reported in 20% of patients treated with idelalisib monotherapy and 5% of patients treated with idelalisib and rituximab. Severe diarrhea/colitis has been reported in 14% of patients treated with idelalisib across clinical trials; therefore, the colitis may not have been related to the addition of lenalidomide. We hypothesize that immune activation triggered by exposure to the biological triplet caused hepatotoxicity observed in this study, as lenalidomide is known to provide T-cell costimulation, suppress regulatory T-cell expansion, and enhance Th1 cytokine production, whereas phosphatidylinositol 3-kinase inhibition can impact both regulatory and effector arms of the immune system, potentially leading to both immune suppression and autoimmunity. Supporting our observation, Smith et al recently reported hepatotoxicity using a similar combination. All 3 agents are commercially available for the treatment of B-cell lymphoma; however, based on the available data, this combination is unacceptably toxic and should be avoided.

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Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukemia: a matched cohort study

In recent years, there has been growing evidence that hospital volume affects survival among patients undergoing a variety of surgical procedures and medical treatments. Whether case volume affects outcomes after chemotherapy among patients with acute myeloid leukemia (AML) remains unknown. Several complications may occur during AML chemotherapy including infections, leukostasis, intracranial hemorrhage, and other bleeding complications, and management of these conditions requires specialized experienced health professionals and resources. Hospitals with higher volumes may be more adept at managing these complications and hence have a lower mortality rates.

We used the Nationwide Inpatient Sample (NIS) database from the years 2009 to 2011 to explore this hypothesis. NIS is the largest all-payer inpatient database available in the United States and is sponsored by the Agency for Healthcare Research and Quality. We identified the study cohort using code V58.11 ( Encounter for antineoplastic therapy) as the principle diagnosis and using the International Classification of Diseases, 9th revision (ICD-9-CM) code 205 for AML as a secondary diagnosis. Hospitals were divided into quartiles (25th, 50th, and 75th), based on the annual number of cases of AML admitted for chemotherapy. Subsequently, they were divided into high-volume centers (>75th percentile) and low-volume centers (<75th percentile) based on a review of similar studies. We used propensity matching with a nearest neighbor-matching algorithm to build a matched dataset for high-volume centers and low-volume centers controlling for covariates affecting outcomes including age, sex, comorbidity (using the Charlson Comorbidity Index), insurance status, income status (in quartiles), hospital size, location, ownership, and day of admissions (weekend vs weekday). Parametric methods for independent samples were used for analyzing the propensity-matched data set as suggested by Schafer and Kang in 2008. Statistical analysis was done using STATA 13.0 (College Station, TX).

An estimated 15 446 hospitalizations were identified during the study period. After propensity matching, 3640 hospitalizations were selected for final analysis. This included 1150 (31%) cases in high-volume centers and 2489 (69%) cases in low-volume centers. The mortality rate was significantly higher in the low-volume (4.97%) vs the high-volume centers (1.59%) (odds ratio, 3.26; 95% confidence interval, 1.98-5.38; P < .001). After removing the elective cases from this cohort, the difference continued to remain significant (3.4% vs 0%, respectively; P < .001). The mean length of stay was similar between the low-volume centers and high-volume centers (14.6 vs 14.2 days; P = .88). Similarly, the mean cost of hospital stay was similar between the 2 groups ($101 945 vs $102 643; P = .96) (Table 1).

Our study demonstrates clear differences in mortality among patients undergoing chemotherapy for AML based on hospital volume. The most striking example for this “volume-outcome relationship” has been seen in certain cancer surgeries like esophagectomy, pancreatectomy, etc., which is possibly a reflection of “practice makes a man perfect.” However, the same relationship has also been shown to be true for medical conditions such as heart failure, pneumonia, and

Table 1. In-hospital outcomes of high-volume vs low-volume centers in a matched cohort of patients with acute myeloid leukemia admitted for chemotherapy

<table>
<thead>
<tr>
<th>Category</th>
<th>High-volume center</th>
<th>Low-volume center</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.59%</td>
<td>4.07%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean length of stay (SD)</td>
<td>14.22 (1.04)</td>
<td>14.59 (2.31)</td>
<td>.88</td>
</tr>
<tr>
<td>Costs of hospitalization</td>
<td>102653 (11242)</td>
<td>101945 (12585)</td>
<td>.96</td>
</tr>
</tbody>
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SD, standard deviation. P values calculated from χ² tests and analysis of variance.

References

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