Paclitaxel-induced sickle cell crisis

NICOLE M. WILSON, JANET L. ESPIRITO, VICENTE VALERO, AND LAJOS PUSZTAI

Sickle cell disease (SCD) comprises several types of genetic disorders that affect the production of red blood cells. Sickle cell anemia occurs when two sickle hemoglobin (hemoglobin S) genes are inherited. Other forms, such as hemoglobin SC disease and β-thalassemia, appear when one sickle hemoglobin gene is inherited in conjunction with a second abnormal hemoglobin gene or when a mutation is inherited that leads to decreased synthesis of β-globin genes. People with sickle cell trait typically have a benign course, despite having a single hemoglobin S gene, since the majority of their hemoglobin is normal.1,2

Sickle cells, unlike normal red blood cells, are more rigid and have a tendency to polymerize when deoxygenated. Damaging complications can occur when these cells obstruct the microvasculature, which can cause tissue ischemia and organ dysfunction. Vaso-occlusive crisis, a type of sickle cell crisis, causes recurrent, painful episodes typically located in the chest, back, abdomen, and extremities. Other disease manifestations include hemolytic anemia, acute chest syndrome, and frequent infections.1

There is little information regarding treatment of breast cancer in patients with SCD. The combination of SCD and cancer is thought to be relatively uncommon, possibly due to the shorter life expectancy of these patients. However, improvements in the management of SCD have led to a longer life expectancy,3 and increasing numbers of cases of malignancy have been reported in the literature.4-12 Thus, information on how to treat these patients is valuable for clinicians. We report a case of...
sickle cell crisis induced by paclitaxel in a woman with breast cancer and previously undiagnosed SCD and describe her tolerance to additional chemotherapy.

**Case report**

A 55-year-old postmenopausal African-American woman had stage IIB (T2, N1, M0) invasive ductal carcinoma of the left breast. A diagnostic needle biopsy indicated that her tumor was negative for both estrogen and progesterone receptors and the human epidermal growth factor receptor type 2 gene amplification. Her medical history was normal. She was not taking any medications and did not report a family history of cancer or other diseases. At the time of diagnosis, she weighed 86 kg. She had mild microcytic anemia, with a hemoglobin of 10.5 g/dL (normal range, 12–16 g/dL) and a mean corpuscular volume of 71 fl (normal range, 82–98 fl). Her total bilirubin, aspartate transaminase, and lactate dehydrogenase concentrations were slightly elevated at 1.2 mg/dL, 673 IU/L, and 1334 IU/L, respectively. Her other blood counts and liver function test values were normal. Systemic staging with a bone scan and computed tomography scans of her chest and abdomen did not reveal any metastatic disease.

The patient underwent segmental mastectomy of her left breast and axillary lymph node dissection that revealed a 4-cm invasive cancer, with 1 of 10 axillary lymph nodes positive for metastatic disease. Her treatment plan included adjuvant chemotherapy with weekly paclitaxel 80 mg/m² i.v. for 12 weeks, followed by four cycles of i.v. fluorouracil, epirubicin, and cyclophosphamide. Laboratory tests before starting this chemotherapy regimen revealed a hemoglobin concentration of 7.3 g/dL, bilirubin concentration of 2.0 mg/dL, and lactate dehydrogenase concentration of 704 IU/L. Her white blood cell count was normal; however, a shift to the left was noted. Her electrolytes and renal and other liver function test values were within normal limits. The patient also had a low-grade fever and hypoxia. Arterial blood gas showed a partial pressure of oxygen of 57 mm Hg (lower limit of normal = 75 mm Hg), which improved with oxygen supplementation through nasal cannula. Results of blood and urine cultures were negative. A computed tomography angiogram of her chest and chest radiograph showed no evidence of pulmonary emboli or infarct but did show areas of consolidation, indicating possible pneumonia. The patient received one unit of packed red blood cells, empirical antibiotics, high doses of opioid analgesics, and muscle relaxants.

The hematology department was consulted. A review of systems confirmed fatigue, back pain, left-sided rib pain, and shortness of breath that worsened on deep inspiration (pleuritic type). On direct questioning about her history of blood disorders, the patient recalled being told that she had sickle cell trait, but denied ever having a sickle cell crisis. Laboratory tests revealed the following concentrations: hemoglobin, 8.7 g/dL; mean corpuscular volume, 76 fl; reticulocyte count, 8.8% (normal range, 0.5–1.5%); bilirubin, 2.9 mg/dL (direct, 0.5 mg/dL; indirect, 2.4 mg/dL); and lactate dehydrogenase, 1716 IU/L. Her iron values were consistent with microcytic anemia, not caused by iron deficiency. Laboratory tests during her 13-day hospitalization were consistent with hemolysis (Table 1). Hemoglobin electrophoresis was performed, which identified the presence of hemoglobin S and hemoglobin C. The patient was diagnosed with hemoglobin SC disease and later discharged from the hospital with as-needed, low-dose oxycodone and baclofen, antibiotics, and folic acid.

Paclitaxel was discontinued and the patient received i.v. fluorouracil, epirubicin, and cyclophosphamide. Laboratory tests before starting this chemotherapy regimen revealed a hemoglobin concentration of 10.5 g/dL, bilirubin concentration of 1.2 mg/dL, and lactate dehydrogenase concentration of 476 IU/L. The patient received prechemotherapy hydration with 1 L of 0.9% sodium chloride injection over two hours, as well as standard pretreatment with dexamethasone, ondansetron, and lorazepam. Darbepoetin was added with each cycle of chemotherapy. Although the patient’s bilirubin value was slightly elevated, likely because of hemolysis rather than liver dysfunction, the dosage of epirubicin was reduced by 25% for the first two cycles to ensure tolerability before advancing to the full dosage. The first cycle was well tolerated, with no complaints other than grade 1 fatigue and grade 1 nausea. The patient complained of back and shoulder pain approximately one week after chemotherapy, but this was adequately controlled with a nonprescription nonsteroidal antiinflam-
Serum Hemoglobin, Bilirubin, and Lactase Dehydrogenase (LDH) Concentrations of Patient

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Hemoglobin (g/dL)</th>
<th>Bilirubin (Direct/Indirect) (mg/dL)</th>
<th>LDH (IU/L)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>10.8</td>
<td>1.2 (NR)</td>
<td>673</td>
</tr>
<tr>
<td>1</td>
<td>7.9</td>
<td>2.0 (NR)</td>
<td>704</td>
</tr>
<tr>
<td>2</td>
<td>8.3</td>
<td>3.0 (NR)</td>
<td>2264</td>
</tr>
<tr>
<td>3</td>
<td>8.1</td>
<td>3.2 (0.6/2.6)</td>
<td>1900</td>
</tr>
<tr>
<td>4</td>
<td>8.1</td>
<td>2.1 (0/2.1)</td>
<td>2093</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
<td>1.7 (0/1.7)</td>
<td>2204</td>
</tr>
<tr>
<td>6</td>
<td>8.0</td>
<td>2.0 (0.4/1.6)</td>
<td>1824</td>
</tr>
<tr>
<td>7</td>
<td>8.2</td>
<td>2.7 (0.7/2.0)</td>
<td>1777</td>
</tr>
<tr>
<td>8</td>
<td>8.3</td>
<td>2.2 (0.4/1.8)</td>
<td>1681</td>
</tr>
<tr>
<td>9</td>
<td>8.3</td>
<td>2.7 (0.5/2.2)</td>
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</tr>
<tr>
<td>10</td>
<td>8.7</td>
<td>2.9 (0.5/2.4)</td>
<td>1716</td>
</tr>
<tr>
<td>11</td>
<td>8.0</td>
<td>2.3 (0.4/1.9)</td>
<td>1586</td>
</tr>
<tr>
<td>12</td>
<td>8.0</td>
<td>1.7 (0.3/1.4)</td>
<td>1553</td>
</tr>
<tr>
<td>13</td>
<td>7.6</td>
<td>1.5 (0.3/1.2)</td>
<td>1446</td>
</tr>
<tr>
<td>14</td>
<td>7.7</td>
<td>1.4 (0/1.4)</td>
<td>1515</td>
</tr>
</tbody>
</table>

*Normal range, 12–16 g/dL.
*Normal range, 0–1 mg/dL.
*Normal range, 313–618 IU/L.
*Before initiating paclitaxel chemotherapy.
*NR = not recorded.

This patient’s initial painful crisis may have been induced by paclitaxel. The mechanism for this is not well-known. In the literature, there are data to suggest that paclitaxel can affect plasma membrane composition through interference with vesicle transport and membrane trafficking pathways. Some reports have cited both paclitaxel and docetaxel as causing erythrocyte apoptosis. Erythrocyte apoptosis is triggered by increased erythrocyte calcium activity, which leads to cell surface exposure of an erythrocyte apoptotic signal called phosphatidylserine. The decreased life span of erythrocytes in patients with SCD has been thought to be caused by a similar mechanism. Other literature has suggested that solubilizing vehicles, such as Cremophor-EL and polysorbate 80, and not the taxanes themselves can lead to altered red blood cell morphology and increased plasma viscosity. Therefore, it is unclear whether the effects are due to paclitaxel or Cremophor-EL or whether alternative taxane formulations, such as docetaxel (in polysorbate 80) or albumin-bound paclitaxel (without Cremophor-EL), would cause a similar effect. Our patient did receive Cremophor-EL-containing paclitaxel.

Shortly following the third cycle of chemotherapy, the patient complained of myalgias and generalized muscle aches that warranted another visit to the emergency department. While we cannot conclude that the patient did not develop another painful crisis due to the chemotherapy, the potential reasons or mechanisms for the poor tolerance during this particular cycle of chemotherapy are unclear and may be multifactorial. After tolerating the first two cycles of chemotherapy at a reduced dose, full-dosage epirubicin was administered for the third cycle. Another potential explanation for these symptoms could be the cumulative nature of adverse effects associated with subsequent cycles of chemotherapy. In addition, some patients may have semipermanent sequela from a previous painful sickle cell crisis. On this occasion, the patient had less dramatic changes in the laboratory test values, with a mild 0.1-mg/dL rise in bilirubin concentration, a moderate 1-g/dL decrease in hemoglobin concentration, and a normal lactate dehydrogenase value. In addition, the pain was less severe with this episode, as symptoms were managed with outpatient medication and did not require hospitalization. Because the patient tolerated the first two cycles, it was unclear whether a chemotherapy-induced painful crisis...
had occurred, and additional precipitating factors should be considered.

While chemotherapy mechanistically contributes to cell apoptosis, initiation of chemotherapy in general may not necessarily be a triggering factor for a painful crisis. A literature review revealed sparse case reports of patients with various forms of SCD with several different types of malignancies, including breast carcinoma, hemangiendothelioma of the bone, renal medullary carcinoma, multiple myeloma, lymphomas, and both chronic and acute leukemias. Good tolerance to several different types of chemotherapy, including specifically, anthracycline-based therapy, as well as successful stem cell transplantation, has been noted. We know of two women with SCD and breast cancer who received cyclophosphamide, methotrexate, and fluorouracil chemotherapy, but we are not aware of any cases in which anthracycline and taxane-based therapy were used for breast cancer. Sickle cell crisis has been reported with the use of granulocyte colony-stimulating factor after chemotherapy. The mechanism for a potential sickle cell crisis induced by fluorouracil, epirubicin, and cyclophosphamide is unknown. Case reports have shown that all three agents—fluorouracil, anthracyclines, and cyclophosphamide—have been well tolerated in patients with SCD. Although infections, changes in body fluid status, and climatic factors have been reported to potentially precipitate a crisis, multiple factors may be involved. To our knowledge, we report the first case of a paclitaxel-induced acute painful crisis in a patient with SCD.

For our patient, application of the Naranjo et al. algorithm indicated a score of four, suggesting a possible relationship between treatment with paclitaxel and painful sickle cell crisis. Causality is always difficult to determine retrospectively in case reports; nonetheless, the correlation of laboratory findings for hemolytic anemia and clinical findings of acute back pain and pulmonary complications after a single dose of paclitaxel in this otherwise healthy woman with hemoglobin SC disease suggests a paclitaxel-induced painful crisis.

**Conclusion**

A patient with breast cancer and SCD had a painful crisis after receiving paclitaxel as part of her chemotherapy regimen.

**References**