Original Study

Everolimus-Induced Hematologic Changes in Patients With Metastatic Breast Cancer

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Abstract

We report on hematologic toxicities encountered during a clinical trial using everolimus for metastatic breast cancer. Anemia, thrombocytopenia, and leukopenia were common but mild. Microcytosis and reduced red cell hemoglobin content were consistently observed during treatment. Although total white blood cell counts remained stable, there was a progressive decrease of lymphocyte percentage over time with a trend for increased neutrophils.

Background: Everolimus, which inhibits the mammalian target of rapamycin (mTOR), is increasingly used in breast cancer and familiarity with its full range of toxicity is critical for practicing oncologists. **Patients and Methods:** We studied hematologic changes in 31 patients with metastatic breast cancer treated in a phase II clinical trial using everolimus. Complete blood counts were collected at baseline, 2 weeks, 4 weeks, every 4 weeks during treatment, and 1 month after discontinuation. Adverse events were defined using Common Toxicity Criteria version 3. Linear mixed models with fixed effects of time and random intercepts and slopes were used to study trends and comparisons were conducted using paired *t* tests. **Results:** Anemia was reported in 22 patients (71%), thrombocytopenia in 17 (55%), and leukopenia in 14 (45%). These were predominantly grade 1 or 2 and did not require dose modification. Red blood cell mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) both decreased significantly over time ($P < .0001$) starting at 2 weeks with no significant change in mean corpuscular hemoglobin concentration (MCHC) ($P = .104$). Both MCV and MCH increased 1 month after treatment discontinuation (P values $< .0001$ and .0003, respectively) indicating reversibility of this effect. Although total leukocyte counts remained largely stable, lymphocyte percentage progressively decreased over time with a trend for increased neutrophils. **Conclusion:** In addition to anemia, leukopenia, and thrombocytopenia, everolimus consistently induces red cell microcytosis and reduced hemoglobin content. Lymphopenia may contribute to immune suppression and increased risk of infection. Familiarity with these hematologic changes is prudent as more patients are treated with this class of drugs.

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Introduction

Increasingly, the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway has emerged as a critical survival pathway in cancer cell growth and survival over the last decade,[1] and inhibitors of mTOR are now frequently used in the treatment of patients with a variety of cancers. In addition, mTOR is a phylogenetically conserved master regulator in a number of critical biologic processes through its largely conserved role in cell growth, nutrition, and energy metabolism.[2,3]

Everolimus, which is an oral inhibitor of mTOR, is approved by the Food and Drug Administration for the treatment of several cancers including renal cell carcinoma,[4] progressive neuroendocrine tumors of pancreatic origin,[5] giant cell astrocytoma,[6] and, most recently, metastatic hormone receptor-positive breast cancer that has become resistant to aromatase inhibitor therapy.[7] Despite the

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established efficacy and value of using everolimus and other mTOR inhibitors in cancer patients, this class of drugs is associated with classic well described toxicities such as mucositis[8] and pneumonitis,[9] in addition to several unfavorable metabolic changes, including hyperglycemia and dyslipidemia.[10] Myelosuppression, which is a well described toxicity of traditional chemotherapeutic agents, can also develop with mTOR inhibition, although it is typically less frequent and not as severe in magnitude. Recently, several articles reviewed the hematologic toxicities associated with mTOR inhibitor use[11,12] with a particular emphasis on describing reduction in cell counts (anemia, thrombocytopenia, or leukopenia). These toxicities are presumed to be related to the antiproliferative effects of mTOR inhibition, but the exact mechanisms are not yet fully characterized.[13]

In this report, we describe hematologic changes encountered during a phase II trial using everolimus for patients with metastatic breast cancer. This was prompted by our observation of a consistent decrease in mean corpuscular volume (MCV) during therapy, which led to further examination of hematologic changes during the trial. With increasing use of this class of drugs in cancer, awareness of these changes is important for the treating oncologist and might shed light on additional potential mechanisms for the anticancer effect of everolimus and similar rapalogs.

Patients and Methods

Patient Data

Complete blood counts (CBCs) including leukocyte differential and red blood cell indices were analyzed from patients enrolled in a phase II trial of combined everolimus with fulvestrant for metastatic breast cancer (clinicaltrials.gov identifier: NCT00570921).[14] Patients were treated with everolimus 10 mg daily along with fulvestrant loading dose regimen: 500 mg on day 1, and 250 mg on day 14, day 28, and monthly thereafter. CBCs, and clinical and biochemical data, were collected at baseline, at 2 weeks, 4 weeks, and every 4 weeks thereafter during treatment. In addition, patients were required to have a CBC 1 month after treatment discontinuation as part of the study safety follow-up. The clinical protocol was approved by the University of Kentucky institutional review board and all patients signed informed consent.

Hematologic Data

Hematologic toxicities (anemia, thrombocytopenia, and leukopenia) were reported according to study protocol using Common Toxicity Criteria (CTC) version 3. Red blood cell indices analyzed included MCV measured in femtoliter (fL), mean corpuscular hemoglobin (MCH) in picograms (pg), and mean corpuscular hemoglobin concentration (MCHC) in grams per deciliter (g/dL). Time trends in total white blood cell (WBC) count and percentage of lymphocytes, neutrophils, and monocytes were recorded and studied.

Statistical Analysis

Linear mixed models with fixed effects of time and random intercepts and slopes were used to study trends of hematologic parameters over time in the 31 patients evaluable during the study.[15] Linear mixed models are useful in analyzing data when repeated measurements are made over a period of time and enable analysis between and within the 31 patients during treatment. Comparisons in hematologic parameters between different time points were conducted using a paired t test and 95% confidence intervals (CIs) were determined. Wilcoxon signed rank test was used to compare the median difference in patient weights (n = 23) at 2 months and nadir weight during treatment compared with baseline. All P values reported are 2-sided.

Results

Anemia, Thrombocytopenia, and Leukopenia

Hematologic toxicities were commonly observed on study treatment. These were recently highlighted in the clinical trial report[14] and are summarized herein in more detail (Table 1). Of the total number of toxicities, 76% of toxicities were Grade 1% and 22% were Grade 2, with 1 Grade 3 toxicity (anemia), which was deemed unlikely related to study treatment. There were no Grade 4 toxicities. Everolimus dose was not adjusted based on blood count changes and the full dose of 10 mg daily was continued unless adjustment was required for other dose-limiting toxicities (most commonly mucositis).

Red Blood Cell Indices

During study conduct, we observed an early and consistent decrease in red blood cell indices, which led us to further analyze MCV, MCH, and MCHC. All 31 evaluable patients experienced a significant decrease in MCV at a rate of −1.587 fL per month (95% CI, −2.025 to −1.148; $P < .0001$; Figure 1A). Similarly, MCH also decreased significantly over time, with a rate of −0.562 pg per month (95% CI, −0.72 to −0.404; $P < .0001$; Figure 1B). Interestingly, the decrease in MCV and MCH started as early as 2 weeks after treatment (Table 2) and persisted for the duration of protocol treatment. Remarkably, 1 month after discontinuation of treatment, there was a significant increase in MCV ($P < .0001$) and MCH ($P < .0003$), indicating that everolimus effect was reversible (Table 3). There was no change in MCHC during the treatment period ($P = .1036$; Figure 1C) or 1 month after treatment discontinuation ($P = .883$; Table 3).

Of particular relevance, and parallel to the change in red cell indices, we also observed a significant decrease in patient weight as early as 2 months after start of treatment (median of −2.7% body weight; $P = .0003$) with further decrease in weight as patients remained on treatment for longer duration (median of −5.9% body weight; $P < .0001$).

White Blood Cells and Differential Count

Using the same linear mixed model, we evaluated the change in total WBC and percentages of lymphocytes, neutrophils, and monocytes over time. There was a trend for decreasing total WBC at a rate of −0.078 per month ($P = .0633$; Figure 2A) with no significant change 1 month after treatment discontinuation (1.055; 95%

Table 1 Everolimus-Induced Hematologic Toxicity (n = 31)

	Grade 1	Grade 2	Grade 3	Total (%)
Anemia	15	7	1	23 (74)
Thrombocytopenia	15	2	0	17 (55)
Leukopenia	11	3	0	14 (45)