Effects of Exercise in Combination With Epoetin Alfa During High-Dose Chemotherapy and Autologous Peripheral Blood Stem Cell Transplantation for Multiple Myeloma

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Purpose/Objectives: To determine the effect of aerobic and strength resistance training and epoetin alfa (EPO) therapy on transfusions, stem cell collections, transplantation recovery, and multiple myeloma treatment response.

Design: Randomized clinical trial.

Setting: A myeloma research and therapy center in the south central United States.

Sample: 135 patients with multiple myeloma, 120 evaluable.

Methods: Random assignment to exercise or usual care groups. All patients received EPO based on an algorithm. Aerobic capacity, using the six-minute walk test, was assessed prior to induction chemotherapy, prior to stem cell mobilization, and following stem cell collection for all patients and before and after transplantation for patients continuing in the study. Data analysis included analysis of variance to compare other outcome variables by groups.

Main Research Variables: Number of red blood cell and platelet transfusions during transplantation, number of attempts at and total number of days of stem cell collection, time to recovery after transplantation, and response to intensive therapy for multiple myeloma.

Findings: Recovery and treatment response were not significantly different between groups after transplantation. The exercise group had significantly fewer red blood cell transfusions and fewer attempts at stem cell collection. Serious adverse events were similar in each group.

Conclusions: Exercise with prophylactic EPO therapy reduces the number of RBC transfusions and attempts at stem cell collection for patients receiving intensive treatment for multiple myeloma.

Implications for Nursing: Exercise is safe and has many physiologic benefits for patients receiving multiple myeloma treatment.

Key Points . . .

➤ Exercise in combination with epoetin alfa therapy reduced the number of transfusions and the number of attempts at stem cell collection while improving aerobic capacity.

➤ Patients receiving chemotherapy and autologous peripheral blood stem cell transplantation can exercise safely.

➤ Nurses should use exercise as an intervention to reduce the need for transfusions and improve stem cell collection.
hemoglobin levels and reduces the need for RBC transfusions in diverse groups of patients with cancer-related anemia (Henry, 2005), particularly patients with multiple myeloma receiving chemotherapy treatment (Barlogie & Beck, 1993). Evidence supports the benefit of exercise in managing fatigue during and after treatment for patients with breast cancer and other solid tumors (Courneya & Friedenreich, 1999; Galvo & Newton, 2005; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Schmitz et al., 2005; Stevinson, Lawlor, & Fox, 2004; Stricker, Drake, Hoyer, & Mock, 2004), as well as for those receiving hematopoietic stem cell transplantsations, including patients with multiple myeloma (Strong, Karavatas, & Reicherter, 2006). Although limited by small sample size, results from a recent randomized controlled trial (Drouin et al., 2006) suggest that exercise increases hemoglobin levels. Women receiving radiation treatment for breast cancer (N = 20) were randomly assigned to aerobic exercise or to placebo stretching during the seven-week treatment period. Hemoglobin increased from 12.3 to 12.4 g/dl in the aerobic exercise group and decreased from 12.3 to 11.8 g/dl in the placebo stretching group (p = 0.009). Peak oxygen intake measures correlated to the final measures for hemoglobin (p = 0.013). The researchers concluded that moderate intensity aerobic exercise may be a safe and economical way to improve fitness and maintain erythrocytes during radiation treatment for breast cancer.

Because exercise increases hemoglobin levels, it also may improve stem cell collection during apheresis procedures. Exercise augments coagulation and fibrinolysis while maintaining the balance in the two processes (Li, He, Blomback, & Hjemdahl, 2007). Exercise has been shown to increase circulating activated platelets (Li et al.) and the change is partially explained by an increase in platelet counts induced by exercise (Ahmadizad, El-Sayed, & MacLaren, 2006; Aldemir & Kilic, 2005). However, no convincing evidence exists that suggests EPO therapy can provide the same benefits for patients with normal or near-normal hemoglobin levels as it does for patients with moderate-to-severe anemia (Steensma & Loprinzi, 2005), and it also is unclear whether EPO, with or without concurrent exercise therapy, improves tumor response to cancer therapy (Steensma & Loprinzi) or recovery after transplantation.

The purpose of the current study was to determine the affect of EPO therapy (short term versus long term) with and without a home-based individualized exercise program that incorporated aerobic and strength resistance training for patients being treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation (PBSC) for multiple myeloma. The endpoints for the study included the number of attempts at and total number of days of stem cell collection, number of RBC and platelet transfusions during the transplantation period, time-to-recovery after transplantation, and response to intensive therapy for multiple myeloma.

<table>
<thead>
<tr>
<th>Exercise (N = 66)</th>
<th>Usual Care (N = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrew from multiple myeloma treatment protocol (n = 2)</td>
<td>Died (n = 1) Withdrew from the study (n = 5)</td>
</tr>
<tr>
<td>Died (n = 1) Withdrew from the study (n = 3)</td>
<td>Died (n = 1) Withdrew from the study (n = 3)</td>
</tr>
</tbody>
</table>

**Figure 1. Enrollment, Attrition, and Group Assignment**

<table>
<thead>
<tr>
<th>Exercise (n = 23)</th>
<th>Usual care (n = 28)</th>
<th>Exercise (n = 35)</th>
<th>Usual care (n = 34)</th>
</tr>
</thead>
</table>

**Figure 2. Treatment Protocol for Total Therapy II Through the Duration of the Study**

<table>
<thead>
<tr>
<th>Short-Term Study</th>
<th>Long-Term Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enroll</td>
<td>VAD</td>
</tr>
<tr>
<td>DCEP</td>
<td>CAD before stem cell harvest</td>
</tr>
<tr>
<td>5 weeks</td>
<td>5 weeks</td>
</tr>
<tr>
<td>3 months</td>
<td>5 weeks</td>
</tr>
</tbody>
</table>

**Note.** In addition to the chemotherapy agents, patients were randomized to receive or not receive thalidomide, with patients taking thalidomide receiving prophylactic low molecular weight heparin.
Methods

Subjects

The sample included patients newly diagnosed with multiple myeloma and eligible for treatment with an intensive treatment protocol that included tandem autologous PBSCT. Inclusion criteria for the study were a new diagnosis of multiple myeloma and an intensive treatment protocol with or without thalidomide. Patients at high risk for pathologic fractures or spinal cord compression were excluded. Other exclusion criteria were major psychiatric illness, microcytic or macrocytic anemia, uncontrolled hypertension, RBC transfusions within the previous two weeks, or EPO therapy within eight weeks prior to study enrollment. The institutional review board at the University of Arkansas for Medical Sciences approved the study.

For a fixed effects two-tailed analysis of variance (ANOVA) design with two levels of care (usual care and exercise) and two levels of duration (short and long term), a power analysis using G*Power 3.0.5 (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that a sample size of 128 participants (64 per group) would have an actual power of 80.14% to detect a moderate partial η² effect size of 0.06.

Research Design

Patients (n = 135) who met eligibility criteria and provided informed consent were randomized to usual care (n = 69) or exercise (n = 66) groups as they were enrolled in the multiple myeloma treatment protocol. Patients were stratified by age (60 and younger versus older than 60) and whether or not they were taking thalidomide as they were randomized to exercise or usual care groups. A total of 120 patients completed the short-term section of the study and were evaluable. The reasons for attrition (n = 15, 11%) are illustrated in Figure 1.

Remaining patients (n = 120) were in the study for about 15 weeks, which included stem cell collection. The first 70 patients who met eligibility for long-term participation (i.e., response to EPO) continued in the study for an additional 15 weeks, which included the first transplantation. Nine patients had no response to EPO (four in the exercise group and five in usual care), and one eligible patient declined continued enrollment, leaving 69 patients to continue the study for about 15 more weeks.

Interventions

The intensive treatment protocol, called Total Therapy II, included induction chemotherapy with vincristine, doxorubicin, and dexamethasone (0.5 mg, 10 mg/m², and 40 mg, respectively); dexamethasone, cyclophosphamide, etoposide, and cisplatin (40 mg, 400 mg/m², 40 mg/m², and 15 mg/m², respectively); and cyclophosphamide, doxorubicin, and dexamethasone (750 mg/m², 15 mg/m², and 40 mg, respectively) for mobilization. The regimen was followed by stem cell collection and repeat treatment with DCEP and high-dose melphalan (200 mg/m²) followed with autologous PBSCT. The interval between each of the treatments was about five weeks. Patients received a second treatment of high-dose melphalan and a stem cell transplantation about three months after the first transplantation. Fifty percent of the patients were randomized to receive thalidomide (400 mg daily) during induction, after transplantation consolidation, and maintenance therapy. Patients randomized to thalidomide received prophylactic low molecular weight heparin (Baloge, 2001). Outpatient treatment was planned and hospital

Figure 3. Investigational Epoetin Therapy Algorithm
patients were advised to take 300 mg of ferrous sulfate orally three times daily, or 325 mg of ferrous gluconate orally three times daily and 250 mg of vitamin C orally once daily.

Patients assigned to the usual care group were advised to follow the written exercise recommendations provided by their physician. The patients were generally advised to remain as active as possible and to try to walk 20 minutes per day. Patients assigned to the exercise group received an individualized exercise prescription, a set of color-coded exercise stretch bands with varying resistance, and a notebook and videotape illustrating the exercises. Strength resistance training was included to strengthen muscles so patients could improve the aerobic component of the exercise program (see Table 1).

### Measurements

Patients faxed weekly activity logs to investigators, which were used, along with periodic personal interviews, to assess compliance with the exercise program for patients in the exercise group and the exercise patterns of patients in the usual care group. Additional objective assessments of all patients included aerobic capacity, using the six-minute walk test (distance, in feet, walked on a level surface in six minutes) and the Borg Scale (Borg, 1998) to determine perceived exertion at each assessment. The six-minute walk test has been shown to be linearly related to maximum metabolic equivalents ($r = 0.687$, $p < 0.001$), supporting its validity and strong test retest reliability (intraclass correlation = 0.97) (Hamilton & Haennel, 2000). The Borg Scale is a simple method of subjectively rating exertion (American College of Sports Medicine, 2001; Borg; Sports Coach, 1997), and the rate of perceived exertion correlates with approximate heart rate. Measurements were obtained for each patient in the study at baseline (prior to induction chemotherapy), prior to stem cell mobilization, and following stem cell collection. Additional measurements were obtained before and after transplantation for each patient continuing the study through the first transplantation.

The numbers of RBC and platelet transfusions during the transplantation period were obtained from the University of Arkansas for Medical Sciences blood bank. All patients received transfusions from the blood bank during their transplants, so it was an accurate source for data. Data on stem cell collection were obtained from the University of Arkansas for Medical Sciences apheresis laboratory. Response to intensive treatment for multiple myeloma was the criterion for evaluation of Total Therapy II, and endpoints were obtained from the Myeloma Institute for Research and Therapy database. Time-to-recovery after transplantation was defined as the number of days before white blood cell recovery (absolute neutrophil count of 2.0 or higher).

### Data Analysis

Data analysis included descriptive statistics to show demographics and outcome variables of interest by groups; $t$ test and chi-square to check for equivalence of groups for age, gender, and race; and ANOVA to compare outcome variables by groups. A significance level of $p < 0.05$ was used for all analyses.

### Results

The groups were equivalent in age, gender, and race (see Table 2). Figure 4 provides a comparison, by groups, of the
means for the walk test measurements and shows a trend toward better exercise performance by the exercise group. Aerobic capacity declined as treatment program intensity increased, but patients assigned to exercise had less of a decline. Additionally, more patients in the usual care group, compared to the exercise group, were unable to perform the walk tests as treatment progressed.

No significant differences between the groups in response to the intensive treatment protocol for multiple myeloma or between the groups recovering after transplantation were found. Hemoglobin levels during the transplantation period were higher for patients in the long-term group than those in the short-term group; however, hemoglobin levels were similar for the long-term and short-term groups at discharge after transplantation. The higher hemoglobin during the transplantation period was expected for the patients in the long-term group because they had received EPO, according to the investigational algorithm, up to the time of transplantation. All groups had equivalent baseline hemoglobin levels before chemotherapy (see Table 3).

The maximum EPO dose was similar for patients in the exercise and usual care groups. Dose adjustments occurred 5, 9, and 13 weeks into the study, and all escalations occurred before stem cell collection (see Table 4).

Fewer attempts were made at stem cell collection for the exercise group compared with the usual care group (Bonferroni adjusted p < 0.025). Differences in hemoglobin level at the time of apheresis do not offer an explanation, with the mean hemoglobin level on the first day of apheresis similar for the two groups (10.8 g/dl [SD 1.3] for the exercise group and 10.9 g/dl [SD 1.2] for the usual care group).

A trend toward fewer RBC and platelet transfusions during the transplantation period occurred in the exercise group compared to the usual care group. When the nine patients who did not respond to EPO were excluded from the analysis, a statistically significant difference in RBC and platelet transfusions between the exercise and usual care groups was found (Bonferroni adjusted p < 0.025) (see Table 5). The number of attempts at and total number of days of stem cell collection also were significantly fewer for the exercise group compared to the usual care group (Bonferroni adjusted p < 0.025) (see Table 6).

Serious Adverse Events

Overall, the incidence of serious adverse events (SAE) was similar between all groups. The most common SAE were fever, hyponatremia, pneumonia, hyperglycemia, deep vein thrombosis (DVT), infection, and neutropenia. Multiple myeloma, chemotherapy, and thalidomide are risk factors for DVT, and questions arise regarding whether EPO,
particularly at higher-than-approved hemoglobin parameters for dosing, may be associated with an increased risk of DVT. With grade 3 or 4 DVT (National Cancer Institute, 2007), confirmed by Doppler scan, the incidence of DVT occurring between enrollment and transplantation was similar between the exercise and usual care groups and between patients taking or not taking thalidomide. DVT occurring in the upper extremities (n = 17) was related to a central venous catheter. DVT also was found to occur in the lower extremities (n = 12). Five patients had a pulmonary embolus, two of which were in the long-term study. The two patients were receiving thalidomide, with one assigned to exercise and one to usual care. The other three patients experiencing a pulmonary embolus were in the short-term study, with two receiving thalidomide—one assigned to usual care and one to exercise—and the other not receiving thalidomide and assigned to the exercise group. Of the patients with DVT, nine (36%) had a history of previous thromboembolism and 10 (40%) had a DVT preceded by hemoglobin of more than 13 g/dl. Four patients reported symptoms of DVT, but a Doppler scan could not confirm the diagnoses. One death in the long-term study was related to pneumonia. Table 7 shows the incidence of SAE and DVT by group.

### Discussion

The current study’s findings suggest that aerobic and strength-resistance training combined with prophylactic EPO therapy benefits patients by reducing the number of RBC and platelet transfusions and the number of attempts at and total number of days of stem cell collection. Hemoglobin levels during the transplantation period were similar for the exercise and usual care groups. However, compared to the exercise group, the usual care group required significantly more RBC transfusions to maintain the same level of hemoglobin, suggesting that exercise had an effect on hemoglobin level. The findings in the current study are, therefore, consistent with others that report the benefit of exercise in raising hemoglobin levels in patients with cancer. The underlying mechanism to explain this benefit is unknown, but the greatest benefit seems to come from exercise in combination with EPO.

Based on the study results, EPO therapy acted with exercise to decrease the number of transfusions among patients receiving high-dose chemotherapy and transplantations as treatment.
Table 6. Number of Attempts At and Total Days of Stem Cell Collection

<table>
<thead>
<tr>
<th>Group</th>
<th>Exercise (N = 23)</th>
<th>Usual Care (N = 28)</th>
<th>Long Term (N = 69)</th>
<th>Exercise (N = 35)</th>
<th>Usual Care (N = 34)</th>
<th>Long Term Versus Short Term</th>
<th>Exercise Versus Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>SD</td>
<td>95% CI</td>
<td>X</td>
<td>SD</td>
<td>95% CI</td>
<td>X</td>
</tr>
<tr>
<td>Total group: Attempts</td>
<td>1.1</td>
<td>0.3</td>
<td>0.8, 1.3</td>
<td>1.4</td>
<td>0.8</td>
<td>1.2, 1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Total days</td>
<td>4.0</td>
<td>2.3</td>
<td>2.6, 5.3</td>
<td>5.3</td>
<td>4.0</td>
<td>4.1, 6.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Table 7. Incidence of Serious Adverse Events (SAE) and Deep Vein Thrombosis (DVT)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Terma</th>
<th>Long Termb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise (N = 23)</td>
<td>Usual Care (N = 28)</td>
</tr>
<tr>
<td>1 SAE</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>More than 1 SAE</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>1 DVT</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>More than 1 DVT</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01
CI—confidence interval; EPO—epoetin alfa; SD—standard deviation

for multiple myeloma. Duration of EPO administration is important in maintaining higher hemoglobin levels during the transplantation period. Patients in the current study who received EPO according to the study algorithm had higher hemoglobin levels during the transplantation period than patients who were in the study only through stem cell collection. Even with EPO therapy, patients in the current study had an average hemoglobin level of 10.8 g/dl during the transplantation period.

The results also suggest that the investigational use of EPO as prophylactic therapy is beneficial for patients with normal or near-normal hemoglobin levels and patients with anemia. Unless baseline hemoglobin was greater than 15 g/dl, all patients in the study received EPO according to the study algorithm just before receiving chemotherapy. Starting EPO therapy before chemotherapy may help prevent chemotherapy-induced anemia, but several weeks of EPO therapy are needed before the benefit is seen (Ortho Biotech Products, 2005). Study results may not be applicable to patients with less myelosuppressive treatment regimens.

Erythropoiesis-stimulating agents (ESAs) were approved by the U.S. Food and Drug Administration (FDA) based on their effectiveness in reducing the need for RBC transfusions in patients receiving chemotherapy for cancer. The current approved labeling for ESAs, including an FDA Black Box Warning, recommends using the lowest dose necessary in patients receiving chemotherapy to avoid the need for blood transfusions. The FDA (2007) also advises that hemoglobin not exceed 12 g/dl. Health risks associated with the use of ESAs in the treatment of anemia for use in patients with advanced breast, head and neck, lymphoid, and non-small cell lung cancers include shortened overall survival or time-to-tumor progression and an increased incidence of thrombotic events (e.g., myocardial infarction, stroke, thrombosis) in patients receiving chemotherapy (FDA).

The incidence of DVT (21%) was high among patients in the current study. The risk of DVT is known to be high with cancer patients receiving chemotherapy (FDA). The current study results may not be applicable to patients with advanced breast, head and neck, lymphoid, and non-small cell lung cancers include shortened overall survival or time-to-tumor progression and an increased incidence of thrombotic events (e.g., myocardial infarction, stroke, thrombosis) in patients receiving chemotherapy (FDA).
The Centers for Medicare and Medicaid Services (CMS) recently limited coverage of ESAs to patients receiving chemotherapy with a hemoglobin level below 10 g/dl with symptomatic ischemia and who cannot be transfused, or below 9 g/dl in patients with cardiovascular disease (Purrough et al., 2007). The American Society of Clinical Oncology (ASCO) expressed concern over CMS’s national coverage that “makes it impossible for physicians to use these agents in a manner consistent with the FDA-approved prescription labeling for these agents,” and, at the request of CMS, ASCO submitted supporting clinical information (Bailes, 2007, p. 2). The FDA’s response was that FDA-approved labeling and the CMS coverage decision were generally consistent (FDA, 2007). CMS asked for new evidence to show that patients receiving chemotherapy for cancer require hemoglobin levels to be above 10 g/dl. ESA therapy is superior to transfusion therapy (Schnell, 2007).

Limitations

The current study is limited by the lack of transfusion criteria (i.e., hemoglobin level or other criteria used to determine whether a transfusion is needed). The analysis may have missed specific disease-related influences on hemoglobin levels. Patients with hemoglobin less than 8 g/dl received RBC transfusions according to the transplantation protocol. Some patients with hemoglobin values above 8 g/dl may have received transfusions because of symptoms or other clinical indications. Although randomization should have distributed disease risks equally for the exercise and usual care groups, patients were not randomly assigned to the short- and long-term groups. However, by taking the first eligible patients, similar numbers of patients from the exercise and usual care groups did take part in the long-term study. The hemoglobin level at which anemia requires transfusions is not well established (Bailes, 2007). Whether patients in the current study received transfusions because of a low hemoglobin level, symptoms, or both is unknown. Regardless of the reason, patients in the usual care group received more transfusions than patients in the exercise group to maintain a similar hemoglobin level.

Implications for Nursing

The results of the current study have important implications for oncology nurses. Although the risks and benefits of ESA therapy are not known, this study has determined that patients receiving high-dose chemotherapy and autologous PBSCT can exercise safely. Therefore, nurses should use exercise as an intervention that may help decrease the need for transfusions. Exercise may also help patients during stem cell collection.

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References


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