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Clinical Oncology [ALERT]

Evidence-based summaries on cancer treatment and research

## ABSTRACT & COMMENTARY

# Bendamustine-rituximab compared with R-CHOP or R-CVP for first-line treatment of indolent NHL

*By William B. Ershler, MD, Editor*

SYNOPSIS: In an international, randomized, non-inferiority trial, bendamustine-rituximab proved comparable in overall response rate when compared with R-CHOP or R-CVP in the management of indolent NHL and mantle cell lymphoma. Progression free and overall survival comparisons remain to be determined. Notably, toxicity profiles were significantly different, with higher rates of reported nausea and vomiting with BR and neuropathy and alopecia with R-CHOP/R-CVP.

SOURCE: Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study. *Blood* 2014;123:2944-2952.

Standard approaches to the treatment of indolent non-Hodgkin's lymphoma (NHL) have evolved over the past few decades with the incorporation of targeting agents coupled with selected chemotherapeutics. This, with advances in supportive care, has resulted in improved outcomes, including survival. Bendamustine is one agent that has gained recent attention because of its demonstrated activity in relapsed NHL, CLL, and in rituximab-resistant NHL.[1-4]

In light of these and other findings, the German Study Group, Indolent Lymphoma (STiL), conducted a phase 3 non-inferiority trial to determine whether 6 cycles of bendamustine and rituximab (BR) were equivalent to 6 cycles of R-CHOP for initial treatment of indolent NHL. Entry criteria included untreated advanced stage disease requiring therapy (rapid progression, disease-related symptoms, bulk, or threatened organ function). The study enrolled 514 subjects and at a median follow-up of 45 months, the median progression-free survival was significantly longer in the BR arm (69.5 vs. 31.2 months; $p <$

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.0001).[5] Treatment with BR was associated with a higher complete response rate, and overall response rates were similar between the two groups. Fewer serious adverse events were reported in the BR arm compared with R-CHOP (19% vs. 29%). Neutropenia, leukopenia, and serious infections were also less common following bendamustine.

With this as background, Flinn and colleagues currently present data from an industry-sponsored validation trial. Its design was a randomized, non-inferiority (NI), international, phase 3 study to determine the efficacy and safety of BR vs. a standard rituximab-chemotherapy regimen, either R-CHOP or R-CVP, in the initial treatment of patients with indolent non-Hodgkin's lymphoma or mantle cell lymphoma. Investigators pre-assigned the standard treatment regimen (i.e., R-CHOP or R-CVP) they considered most appropriate for each patient. Thereafter, patients were randomized to receive BR (n = 224) or standard therapy (R-CHOP/R-CVP, n = 223) for 6 cycles. The data indicated that BR was non-inferior to R-CHOP/R-CVP, as assessed by the primary endpoint of complete response rate (31% vs. 25%, respectively; $p$ = .0225 for NI [0.88 margin]). The overall response rates for BR and R-CHOP/R-CVP were 97% and 91%, respectively ($p$ = .0102). Incidences of vomiting and drug-hypersensitivity reactions were significantly higher in patients treated with BR ($p < .05$), and incidences of peripheral neuropathy/paresthesia and alopecia were significantly higher in patients treated with standard therapy regimens ($p < .05$).

## Commentary

The data support the conclusion that BR is non-inferior to standard therapy with regard to clinical response with an acceptable safety profile. Whether the combination is actually superior will not be evident without longer follow-up and a comparison of progression-free survival, overall survival, and the incidence of long-term toxicities. Oncologists are very familiar with the nuances of R-CHOP (and R-CVP) management, and it is notable that toxicity profiles were sufficiently different with BR. For example, BR-treated patients had a higher rate of significant lymphopenia, whereas R-CHOP/R-CVP was associated with increased neutropenia. BR was also associated with a slightly increased risk of opportunistic infections and nausea but decreased neuropathy and alopecia compared with R-CHOP/R-CVP. Although follow-up data are anticipated and may prove superiority of one approach over the other, clinical oncologists can be reassured that BR may be a suitable alternative to R-CHOP or R-CVP and treatment decisions may be based on factors including scheduling, ease of administration, and comorbidities.

["The data support the conclusion that BR is non-inferior to standard therapy with regard to clinical response with an acceptable safety profile."]

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## ABSTRACT & COMMENTARY

# Yoga for Mood, Fatigue, and Inflammation in Breast Cancer Survivors

***By German H. Rodriguez, MD***
*Attending Physician, West Park Medical Group, New York, NY*
**Dr. Rodriguez reports no financial relationships relevant to this field of study.**

*Synopsis: Breast cancer survivors participating in a 12-week yoga program reported decreased fatigue, increased vitality, and improved sleep on multiple scoring systems, but no impact on depressive symptoms. Increased time spent doing yoga led to greater improvements in inflammation, mood, and fatigue.*

Source: Kiecolt-Glaser JK, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: A randomized controlled trial. *J Clin Oncol*. 2014;32:1040-1049.

In 2010, an estimated 2,829,041 women were living with breast cancer in the United States. Breast cancer affects women of many different age groups. Due to widespread implementation of breast cancer screening, a majority of these are diagnosed at a very early stage. According to the National Cancer Institute, the 5-year survival for localized breast cancer is 98.6%.[1] Cancer patients tend to have lower exercise tolerance and depressed mood. Many factors could be implicated in this common scenario, but the more relevant question lies in what we can do to help these patients continue to lead full lives. Kiecolt-Glaser et al proposed a regimen of supervised yoga as a way to improve mood and decrease fatigue in patients with breast cancer.[2]

### Study Design

The study investigators designed a randomized, controlled trial in which a 12-week Hatha yoga intervention was compared to a wait-list control group. Two hundred stage 0 to IIIA female breast cancer survivors ranging from age 27 to 76 years were recruited. All participants had completed cancer treatments within the past three years, and it had been at least three months since surgery, adjuvant therapy, or radiation. Any patient with a prior history of breast cancer, other types of cancer (except skin cancer), anemia, diabetes, chronic obstructive pulmonary disease, uncontrolled hypertension, evidence of liver or kidney failure, symptomatic ischemic heart disease, autoimmune or inflammatory diseases, cognitive impairment, and alcohol/drug abuse were excluded. Patients who reported > 5 hours of vigorous exercise or who had practiced yoga within the past 6 months also were excluded.

Each patient was stratified based on her cancer stage as well as whether she had received radiation therapy. Afterward, the participants were randomly assigned to either the yoga group or the control group. The data manager did not have any patient contact, and patients were asked not to mention their group to any study personnel. The lab technicians were blind to all data.

All study participants underwent assessments at baseline, immediately post-treatment, and 3 months post-treatment. At each visit, fasting blood samples were obtained to measure interleukin-6, interleukin-1B, and tumor necrosis factor alpha. Multiple well-validated questionnaires evaluated other important quality-of-life measures: degree of fatigue in the last week (MFSI-SF), vitality over the last month (SF-36), depressive symptoms in the last week (CES-D), sleep quality over the last month (PSQI), perceived support (ISEL), frequency and duration of various physical activities (CHAMPS), and foods and beverages consumed in the past 90 days.

The women who were assigned to the Hatha yoga intervention group participated in two 90-minute sessions per week. Twenty-four specific poses were included in the study protocol. A senior Hatha yoga instructor conducted the initial group to improve adherence to the specific poses. The video of this initial session was used to train the six other instructors. All instructors were certified by the Yoga Alliance.

### Results

Baseline demographic characteristics were very similar in the two groups. They also reported similar degrees of physical activity and feelings of fatigue at baseline. Of the original 200 participants, 186 completed the study: 96 in the yoga group and 90 in

the control group. There was no baseline difference of the study outcomes in the two groups. The intervention group attended a median of 19 of 24 possible classes, with an average of 24.69 minutes of yoga per day during the 12-week study period.

### Intervention Effects on Fatigue, Vitality, and Depressive Symptoms

There was no difference between the two groups at the immediate post-treatment visit (6.1 vs. 10.3; $p$ = 0.058), but mean fatigue was significantly lower in the yoga group at the 3-month post-treatment visit (5.4 vs. 12.4; $p$ = 0.002).

The average vitality score was higher in the yoga group at the immediate post-treatment visit (58.7 vs 51.6; $p$ = 0.01) and at the 3-month post-treatment visit (58.1 vs 51.6; $p$ = 0.01).

Depressive symptoms were not significantly different at either the immediate post-treatment visit or the 3-month post-treatment visit.

### Intervention Effects on Inflammation

There was no significant difference between groups at the baseline visit or the immediate post-treatment visit of all three measured cytokines. At 3 months, the yoga intervention group had significantly decreased cytokine levels compared with the control group. Mean values of TNF-a decreased by 13% ($p$ = 0.027), IL-6 decreased by 16% ($p$ = 0.027), and IL-1 decreased by 20% ($p$ = 0.037). Secondary analysis showed that the frequency of yoga practice had a significant impact on cytokine levels. At 3 months post-treatment, a 10-minute per day increase in yoga practice was associated with a 5% decrease of IL-6 ($p$ = 0.01) and an 8% decrease of IL-1B ($p$ = 0.03).

### Health, Behavior, and Support

There was no change in the two groups in diet, body mass index, weight, or social support throughout the study. The yoga group patients did report a significant improvement in sleep quality and decreased sleep disturbance ($p$ = 0.03).

### Commentary

Yoga's popularity has increased dramatically in the past 10 years. By some estimates, there were 4 million Americans practicing yoga in 2004, which increased sharply to about 20 million as of 2011.[3] According to the National Center for Complementary and Alternative Medicine, yoga is the sixth most commonly used alternative therapy in the United States.[4] The potential benefits of yoga have been studied for a multitude of reasons, including depression, pain, and several quality-of-life measures in cancer patients.

This study effectively investigated the impact of a yoga intervention in patients with breast cancer and compared it to a similar group who did not practice yoga. They evaluated multiple well-validated measures of quality of life and three inflammatory markers. There was a significant reduction in levels of fatigue and inflammatory markers and an increase of vitality in the yoga intervention group. Also, these patients reported improved quality of sleep. There was no impact on depressive symptoms.

Subclinical inflammation has been proposed as a risk factor for developing chronic disease and disability among older adults.[5] In addition, studies have shown that cancer survivors have a greater risk of developing secondary cancers and other chronic diseases such as diabetes, cardiovascular disease, and osteoporosis.[6] Chronic inflammation has been proposed as an integral component in the development of fatigue and subsequent declines in physical function.[7]

It is unclear if we should recommend yoga for depressive symptoms. The results of this study did not show any impact on depressive symptoms. There have been multiple studies evaluating the impact of yoga on depressive symptoms. Overall, the findings have been inconclusive, as some studies have found a significant positive impact and others have failed to emulate these results. Many of the studies that have shown that yoga may have a positive impact on depressive symptoms have involved small samples with mixed methodological quality.[8,9]

So what's the bottom line? Should we recommend yoga to our breast cancer patients as an adjuvant therapy? Can these results be extrapolated to other patient populations with other types of cancers or other chronic diseases?

We should encourage yoga practice as an adjuvant therapy to our patients with a few caveats. Some of our patients with chronic conditions may not have the habit of practicing any form of physical activity. We should advise patients to join classes that will provide them with graded exercises that are appropriate for their level of conditioning and degree of flexibility to avoid potential injuries. This is especially important in patients who have bony metastasis, as they have a higher risk of pathologic fractures. Many patients may be apprehensive to start practicing yoga if they have not been physically active for a prolonged period. Some studies have found yoga to be superior to other forms of conventional physical activity.[8] Regardles of their health status, it is important for all yoga

participants to be conscious of their own bodies' abilities and restrictions to ensure that they practice safely. When practiced appropriately, yoga can be very well tolerated. Patients should be aware of their individual skill levels to avoid the risks of overstretching, strains, fractures, overheating, dehydration, and decreased blood glucose levels.[10]

The patients included in this study did not practice any form of habitual exercise. It remains to be seen if patients who are frequently physically active and have a diagnosis of breast cancer will also have lower rates of inflammation and improved quality-of-life measures when compared to their more sedentary counterparts.

It has been postulated that yoga enhances health via multiple mechanisms, including increased endorphin release, decreased sympathetic tone, increased parasympathetic tone, and increased melatonin.[11]

All patients included in this study had undergone some form of conventional therapy. Whether yoga has a similar impact on patients who have opted not to undergo some form of conventional therapy is unknown.

A recent study by Chandwani et al examined the impact of a 6-week yoga program in patients who were undergoing radiation therapy.[12] The study also showed decreased levels of fatigue in the yoga intervention group. Instead of measuring inflammatory markers, they measured cortisol levels. The yoga intervention group had significantly decreased cortisol levels. This could represent an alternate mechanism through which yoga has beneficial effects on breast cancer patients. Patients who had other comorbidities were excluded from the study.

We should discuss the importance of managing some of the conditions that frequently accompany cancer and its treatment prior to promoting the potential benefits of yoga.

The study sample was small and, even though the results were positive, the impact of yoga should still be evaluated in larger population-based clinical trials. Due to the multitude of cancers that are commonly diagnosed in the United States, we cannot say for certain that yoga will have similar benefits in any other type of cancer, but if the patients are chosen carefully and advised appropriately, yoga could be an important part of how we manage cancer in the future.

It is unclear why there was no impact on depressive symptoms, as other studies have shown a positive impact on depressive symptoms. This potentially could be related to the small sample size. Fatigue and depression symptoms were not used as part of the inclusion criteria, so women who were less fatigued and less depressed had less room to show positive changes. Previous studies have found that yoga increases serotonin levels.[11] This could be a potential mechanism by which yoga impacts depressive symptoms.

Lastly, we do not know how long the positive results of this study will continue to bestow benefits on patients. Subsequent studies should consider evaluating the long-term impact of yoga on survival and other important outcomes. This trial showed that yoga had a positive impact on inflammation, fatigue, sleep, and vitality in the evaluated study participants in a dose-dependent fashion. Yoga is a simple intervention that we should have in our repository when we guide our patients through the struggles brought on by breast cancer and other forms of chronic disease.

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## ABSTRACT & COMMENTARY

# Addition of Bevacizumab for Treatment of Platinum-resistant Recurrent Ovarian Cancer

*By William B. Ershler, MD, Editor*

Synopsis: In a trial comparing chemotherapy alone to chemotherapy plus bevacizumab in the treatment of patients with platinium-resistant ovarian cancer, the combination resulted in improved response rates and progression-free survival (PFS) and without a high rate of added toxicity. Whether bevacizumab alone would provide comparable improvements was not assessed but remains an important question for future trials.

Source: Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308.

Platinum-resistant ovarian cancer, defined as disease relapse within 6 months after platinum-containing therapy, has a notoriously poor prognosis, with a median overall survival (OS) of approximately 12 months.[1] At the time of first relapse, approximately 25% of patients have platinum-resistant disease, and eventually nearly all patients with recurrent disease develop platinum resistance. Previous studies have demonstrated that the most active single agents in the platinum-resistant setting are pegylated liposomal doxorubicin (PLD), paclitaxel, and topotecan.[2-4] However, combining these chemotherapeutic agents has been shown to increase toxicity without any additional benefit.[2,5,6] Because of the poor prognosis for patients with platinum-resistant disease, new treatment strategies are needed. One approach currently being investigated is the use of biologic agents, both as monotherapy and in combination with chemotherapy. Bevacizumab is an inhibitor of vascular endothelial growth factor (VEGF) and has shown activity in platinum-resistant ovarian cancer.[7,8]

Pujade-Lauraine and colleagues conducted the AURELIA trial (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer), an open-label, randomized, phase III trial to investigate the effects of combining bevacizumab with chemotherapy in patients with platinum-resistant recurrent ovarian cancer. The primary outcome was investigator-assessed progression-free survival (PFS) by RECIST criteria. Secondary endpoints included objective response rate (ORR), overall survival (OS), safety, tolerability, and quality of life (QoL).

All patients (n = 361) were enrolled between October 2009 and April 2011 and had histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within 6 months of completing ≥ 4 cycles of initial platinum-based therapy, thereby meeting criteria for platinum-resistant disease. Additional eligibility criteria included: age ≥ 18 years, ECOG performance status ≤ 2, and acceptable liver, renal, and bone marrow function. Patients who received more than two prior treatment regimens and those with refractory disease (progression during previous platinum-containing therapy) were excluded. Additionally, due to the previously reported increased incidence of GI perforation with the use of bevacizumab, patients with a history of bowel obstruction, abdominal fistula, intra-abdominal abscess, rectosigmoid disease involvement by pelvic examination, or bowel involvement on CT scan were also excluded. Additional exclusion criteria included: abdominal surgery within 4 weeks of enrollment, untreated CNS disease, history of thrombotic or hemorrhagic disorders within 6 months of enrollment, uncontrolled hypertension, non-healing wounds or ulcers, and uncontrolled cardiovascular disease.

At the time of enrollment, investigators selected a chemotherapy regimen for each individual patient basis. Regimens included: paclitaxel 80 mg/m$^2$ IV on days 1, 8, 15, and 22 every 4 weeks (n = 115); PLD 40 mg/m$^2$ IV on day 1 every 4 weeks (n = 126); and topotecan 4 mg/m$^2$ IV on days 1, 8, 15 every 4 weeks or 1.25 mg/m$^2$ on days 1-5 every 3 weeks (n = 120). All patients were then randomly assigned to either chemotherapy alone (n = 181) or chemotherapy with bevacizumab 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks in patients receiving topotecan every 3 weeks) (n = 179). Treatment was continued until disease progression, toxicity, or patient withdrawal. At the time of disease progression, patients in the chemotherapy alone arm were allowed to cross over to single-

agent bevacizumab, and patients receiving both chemotherapy and bevacizumab received standard-of-care treatment (without bevacizumab).

Response was assessed at baseline and every 8 weeks using either CT or MRI, and safety and tolerability were evaluated prior to each cycle. Patients were observed for ≥ 12 months. Median duration of follow-up was 13.9 months in the chemotherapy alone arm and 13.0 months in the chemotherapy-bevacizumab arm.

There was a significant improvement in PFS in patients who received bevacizumab when compared to those who received chemotherapy alone (two-sided unstratified log-rank test: $p < 0.001$; HR 0.48; 95% CI 0.38 to 0.60). Median PFS was 6.7 months (95% CI 5.7 to 7.9 months) in the chemotherapy plus bevacizumab arm, compared to 3.4 months (95% CI 2.2 to 3.7 months) in the chemotherapy-alone arm. This was seen in all treatment groups, independent of chemotherapy regimen.

Response was evaluated by RECIST in 287 patients. The ORR was 11.8% in the chemotherapy-alone group, compared to 27.3% in the chemotherapy plus bevacizumab group ($p = 0.001$). There was no statistically significant difference in OS between the two groups (HR 0.85; 95% CI 0.66 to 1.08). Median OS was 13.3 months (95% CI 11.9 to 16.4) in the chemotherapy-alone group versus 16.6 months (95% CI 13.7 to 19.0).

Significant adverse events occurred more frequently in the chemotherapy-bevacizumab group (57% vs. 40.3%). GI perforation occurred in four patients (2.2%) who received bevacizumab and in no patients who received chemotherapy alone. There was an increased incidence of grade ≥ 2 hypertension (20% vs. 7%) and proteinuria (2% vs. 0%) in the chemotherapy-bevacizumab group. Grade ≥ 3 hematologic toxicity was seen equally in both treatment groups.

## COMMENTARY

Platinum-resistant ovarian cancer has a poor prognosis, and new treatment modalities are desparately needed. The AURELIA trial is the first randomized phase III study investigating the addition of bevacizumab to standard chemotherapy for patients with platinum-resistant ovarian cancer. The results demonstrate a clear advantage in both progression-free survival and overall response rate with the addition of bevacizumab without a striking increase in toxicity. Overall survival was not influenced, but the frequent cross over to bevacizumab regimens in those who progressed on chemotherapy alone makes this difficult to interpret. Further, there were no unusual or unexpected toxicities with combined bevacizumab-chemotherapy. The study provides a logical "next-step" in the treatment of platinum-resistant ovarian cancer. As we learned from prior from earlier experience with bevacizumab, caution should be raised in patients at risk for perforation including those with significant pre-existing gastrointestinal disease and/or abdominal abscess. Whether bevacizumab-chemotherapy combinations prolong overall survival in this setting will be difficult to prove (i.e., compared to chemotherapy alone), but improved response rate and progression-free survival provide reasonable hope that such would be the case. There is of course, the possibility that bevacizumab alone would provide comparable response rates and progression-free survival as when combined with chemotherapy. This comparison, not included in the AURELIA trial, would seem a logical question for clinical trial.

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**Upon completion of this educational activity, participants should be able to:**

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

## Continuing Education Questions

**1. In the trial reported by Flinn and colleagues, bendamustine-rituximab was shown to be non-inferior to R-CHOP/R-CVP in the treatment of indolent NHL and mantle cell lymphoma in which of the following parameters?**
a. overall response rate
b. progression-free survival
c. overall survival
d. all of the above

**2. Yoga has been found to have a significant impact on which of the following?**
a. fatigue
b. depressive symptoms
c. sleep
d. both a and c
e. all of the above

**3. In the AURELIA trial of regimens utilizing both bevacizumab and chemotherapy compared to chemotherapy alone, improvements were observed for which of the following outcomes?**
a. five-year survival
b. progression-free survival
c. overall survival
d. all of the above
e. none of the above

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