Published in final edited form as:

Leuk Lymphoma. 2012 April ; 53(4): 718–720. doi:10.3109/10428194.2011.623256.

Cardiac toxicity associated with bevacizumab (Avastin) in combination with CHOP chemotherapy for peripheral T cell lymphoma in ECOG 2404 trial

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Introduction

Most patients with peripheral T Cell lymphoma (PTCL) relapse after initial anthracycline based (CHOP) treatment with a 5-year overall survival (OS) of > 30 – 50% [1]. Vascular endothelial growth factor (VEGF-A) is strongly expressed in PTCL and serum concentration of VEGF is an independent predictor of poor outcome [1 – 3]. Gene expression profiling studies in PTCL have also reported that VEGF is significantly over expressed in PTCL supporting the concept that antiangiogenesis may be a therapeutic option [4].

Bevacizumab (Avastin), an anti-angiogenic agent, is a humanized monoclonal antibody directed against VEGFA and FDA approved for lung, colorectal, breast and brain cancers. E2404 study evaluated the combination of bevacizumab and CHOP (A-CHOP) followed by maintenance bevacizumab in patients with newly diagnosed PTCL. Due to the reported 3.8% incidence of cardiac failure associated with bevacizumab in patients with metastatic breast cancer (MBC) previously exposed to anthracyclines (Avastin package insert), cardiac function (ejection fraction) was prospectively monitored by echocardiography. We report on increased cardiac toxicity with A-CHOP observed in E2404. Results of the overall study will be reported in a separate publication.

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Patients and methods

Untreated PTCL patients older than 18 years with baseline cardiac left ventricular ejection fraction (EF) > 50% were eligible. Relevant exclusion criteria included clinically significant cardiovascular disease or peripheral vascular disease, including myocardial infarction, unstable angina (within 6 months prior to registration), NYHA Grade II or greater congestive heart failure, uncontrolled hypertension or a history of stroke within 6 months.

Patients were treated with bevacizumab (15 mg/kg) and standard dose CHOP chemotherapy administered every 21 days for 6 – 8 cycles and those who achieved a complete response, partial response or stable disease received maintenance therapy with bevacizumab (15 mg/kg) every 3 weeks for 4 cycles. Cardiac function was monitored prospectively with EF determination at baseline, and at completion of 6 cycles A-CHOP prior to the start of bevacizumab maintenance. For patients eligible to receive bevacizumab maintenance, EF was required to be > 50%. As the study was ongoing at the time of this report, we reviewed toxicity data (coded according to CTCAE Version 3.0.) for patients completing at least 6 cycles of A-CHOP.

Results and discussion

Between July 2006 and March 2009, 44 patients were treated on protocol. Median age was 59 years (range 19 – 81). Thirty patients received at least 6 cycles of A-CHOP, and within this group, 17 patients also received maintenance bevacizumab. As per study design, EF was assessed for all patients post 6 cycles A-CHOP. One or more designated cardiac events (total 8) were reported in 6 of 30 (20%) patients (90% CI: 9.1 – 35.7%), as summarized in Table I. One patient developed grade 2 ventricular tachycardia after 8 cycles of A-CHOP during cycle 5 of maintenance bevacizumab. Congestive heart failure (CHF), defined as grade 2 – 4 left ventricular dysfunction (LVD) was reported in 5 of 30 (17%) patients (90% CI: 5.6 – 34.7%) who were subsequently taken off study: 4 pts developed symptomatic CHF with grade > 3 LVD after 6 cycles of A-CHOP (including one after cycle 2 of maintenance bevacizumab) and 1 after 8 cycles of A-CHOP. Medical management of CHF was required in all patients, including a ventricular assist device in one patient with concomitant grade 4 arrhythmia.

This rate of CHF is higher than the reported rates of cardiomyopathy from doxorubicin (typically 1% to 2% for a cumulative doxorubicin dose below 300 mg/m², 7% at 575 mg/m², and 21% at > 700 mg/m²) and higher than those reported in studies evaluating R-CHOP or CHOP alone in patients with diffuse large B cell lymphoma (DLBCL)[5,6]. The LVD improved to baseline within 6 months of discontinuing bevacizumab in 4 of 5 patients.

Our cooperative group study has limitations since EF determination was according to individual institutional echocardiography protocols and not centrally reviewed. In addition, the ability to detect a cardiac event may vary among the institutions, which could result in biased adverse event recording. Also, the significance of low-grade events (grade 1 – 2) is not clear, and baseline cardiovascular risks, such as cholesterol, diabetes, thyroid disease and lung conditions were not prospectively evaluated. Additionally, due to limitations of study design, we cannot discern if there is incremental toxicity for patients who received > 300 mg/m² of doxorubicin.

Bevacizumab as a single agent has not been associated with increased cardiac toxicity. Data suggest that MBC patients who have had anthracycline exposure prior to bevacizumab may have an increased incidence of CHF[7]. Limited data exist regarding the incidence of cardiac toxicity when bevacizumab is used in conjunction with anthracyclines and emerging data suggest an increased risk in both solid tumors and lymphomas. A phase II study in

metastatic soft tissue sarcoma with doxorubicin followed by bevacizumab reported that 6 of 17 (35%) patients who received total doxorubicin dose exceeding 300 mg/m² developed grade 2 or greater cardiac toxicity, despite the use of dexrazoxane[6]. The E2104 trial evaluated bevacizumab in combination with an anthracycline containing regimen as adjuvant therapy for breast cancer[8]. At a median follow-up of 14.6 months, 14% of patients experienced asymptomatic EF decrease of > 10%. While a small pilot study evaluating bevacizumab plus R-CHOP on 13 patients with DLBCL did not report on cardiac events [9], increased cardiac dysfunction was reported in a larger experience by Southwest Oncology Group (Study S0515). In this phase II trial, 20% of patients (n > 64) developed grade 2 or 3 LVD when treated with R-CHOP and bevacizumab for advanced stage DLCL[10].

There is scant data on the long-term consequences of the cardiac events. Cardiac dysfunction in our study was reversible after bevacizumab was discontinued and supports the concept that bevacizumab may lead to myocardial stunning without overt permanent damage[11]. The relationship of the combination of bevacizumab and doxorubicin in the development of cardiac dysfunction is not clear. Bevacizumab may lead to weakened repair mechanisms after myocardial damage. VEGF has a role in the repair of endothelial cells and nitrous oxide production[12]. The anti-VEGF effect of bevacizumab may decrease endothelial cell renewal capacity, expose pro-coagulant subendothelial tissue and decrease production of nitrous oxide that is associated with vasoconstriction and increased platelet aggregation and with adhesion to vascular endothelium. Bevacizumab may interfere with the development of collateral circulation, a compensatory mechanism for obstructive arterial disease[13]. Data from mouse models also suggest that VEGF plays a role in the repair of myocardial damage. Cardiomyocyte specific deletion of VEGF genes in mouse models resulted in reduced coronary microvessels, thinning of ventricular walls and decreased contractile function[14]. Although in our study, grade > 3 hypertension was not reported in patients who developed grade > 3 cardiac events, patients treated with bevacizumab may have a significantly increased risk of developing high-grade hypertension which could potentiate cardiac ischemia[15].

In conclusion, our observation supports the emerging body of literature that the concurrent administration of the combination of the angiogenesis inhibitor bevacizumab with anthracycline is associated with increased risk of LVD, albeit reversible. While the long term impact is unknown, it is important for physicians to recognize the potential risk of using bevacizumab in combination with doxorubicin and exercise caution with close monitoring when incorporating promising FDA approved agents for off label use in combination with other chemotherapy agents without controlled prospective clinical trials.

Acknowledgments

This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D., Chair) and supported in part by Public Health Service Grants CA21115, CA23318, CA66636, CA21076, CA16116, CA13650 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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Table 1

Characteristics of patients with cardiac events.

Age	Gender	Stage	IPI	Toxicity (Grade)	Event in Relation to Rx
62	M	II	3	Ventricular tachycardia (2)	8 X A-CHOP > Maintenance
59	M	III	2	Left ventricular dysfunction (3)	6 X A-CHOP
69	F	IV	5	Left ventricular dysfunction (3)	6 X A-CHOP
				Elevated troponin (2)	
81	M	IV	3	Left ventricular dysfunction (3)	6 X A-CHOP
59	M	IV	2	Left ventricular dysfunction (2)	6 X A-CHOP > Maintenance
63	F	IV	2	Left ventricular dysfunction (4)	8 X A-CHOP
				Arrhythmia (4)	

IPI, International Prognostic Index; A-CHOP, Avastin-cyclophosphamide, doxorubicin, vincristine, prednisone).