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Clinical Commentary

Incidence and management of edema associated with trebananib (AMG 386)

HIGHLIGHTS

- Trebananib targets angiogenesis by inhibiting angiopoietin 1 and 2.
- A rare complication of trebananib is edema.
- The proposed mechanism as well as the diagnosis and management of edema are discussed.

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Introduction

Trebananib (formally known as AMG 386; Amgen; Thousand Oaks, CA, USA) is a peptide-Fc fusion protein (or peptibody) that targets angiogenesis by inhibiting the binding of both angiopoietin 1 and 2 to the Tie2 receptor [1]. This investigational agent has demonstrated anti-angiogenic activity in multiple preclinical models [2]. Dual inhibition of angiopoietin 1 and 2 seems to be superior to selective angiopoietin 2 targeting in certain contexts [3]. Several clinical trials have reported on the efficacy and safety of trebananib, causing only mild and reversible adverse events (AE) [4,5]. In a phase I trial of trebananib, one patient with advanced refractory epithelial ovarian cancer (EOC) achieved a partial response as well as a durable decrease in her CA-125 [4]. A phase II randomized trial has since evaluated weekly paclitaxel 80 mg/m^2 (3 weeks on/1 week off) plus weekly trebananib 10 mg/kg, trebananib 3 mg/kg, or placebo in 161 patients with recurrent EOC, with progression-free survival (PFS) as the primary endpoint [5]. The median PFS with trebananib was 7.2 months compared to 5.7 months, respectively, versus 4.6 months with placebo (HR for trebananib arms combined, 0.76; 95% CI, 0.52–1.12; P = 0.165), with evidence of a significant dose–response effect (P = 0.037). The most common grade ≥3 AE was hypokalemia with both doses of trebananib (12% and 11% for 10 mg/kg and 3 mg/kg, respectively, vs 4% for placebo).

In contrast to other anti-angiogenic agents such as the vascular endothelial growth factor (VEGF) inactivating agent bevacizumab, trebananib has not been associated with an increased risk of hypertension and bowel perforation. During the early development of bevacizumab, bowel perforation was identified as a clinically significant toxicity among EOC patients. This generated much controversy and even altered clinical trial design [6]. A Clinical Commentary similar to this one discussed this complication associated with bevacizumab early in its development and was helpful in educating clinicians and investigators [7]. Now, the risk of bowel perforation associated with bevacizumab is well delineated [8].

Recently, edema has been identified as a unique side effect of trebananib. The purpose of this Commentary is to review the existing data attributing edema to trebananib in solid tumors including EOC. We additionally outline emerging management strategies based on our personal experience and review the literature of this rare complication, as phase III trials investigating this agent in EOC are still ongoing.

Clinical development of trebananib in ovarian cancer

A phase Ib study of trebananib in combination with paclitaxel and carboplatin demonstrated that this combination is tolerable in high-risk EOC patients [9]. Few AEs were reported during the trebananib maintenance phase of this front-line study with 1% of patients experiencing grade 3 or worse localized edema. In another phase Ib study of trebananib combined with either pegylated liposomal doxorubicin (PLD) or topotecan in patients with advanced EOC, no dose-limiting toxicities occurred in the cohorts with trebananib while evidence of antitumor activity was suggested based on objective responses [10]. Three phase III clinical trials (*Tr*ebananib *In Ova*rian Cancer-1 or TRINOVA-1 [NCT01204749], TRINOVA-2 [NCT01281254], and TRINOVA-3 [NCT01493505]) are evaluating trebananib in EOC, primary peritoneal (PPC) and fallopian tube cancers (FTC). TRINOVA-1 is evaluating paclitaxel in combination with either trebananib or placebo in previously treated patients with EOC, PPC, or FTC. Eligible patients must have received ≤3 prior chemotherapy regimen(s) and had a platinum-free interval <12 months from first-line platinum-based therapy. The initiation date was October 2010, after recruiting 919 patients the trial was closed and the estimated primary completion date is late 2013. TRINOVA-2 is evaluating PLD in combination with either placebo or trebananib in previously treated patients with EOC, PPC, or FTC. The eligibility for the TRINOVA-2 trial is similar to TRINOVA-1. This study was initiated in March of 2011 and the primary study completion is planned for 2015; of note, TRINOVA-2 was suspended in

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Table 1A
National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 reporting of edema [13].

GRADE	1	2	3	4	5
Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference: swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference: readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation of normal anatomic contour	>30% inter-limb discrepancy in volume: lymphedema; gross deviation from normal anatomic contour interfering with ADL	Progression to malignancy (i.e. lymphangiosarcoma): amputation indicated; disabling	Death
Edema: trunk/ genital	Swelling or obscuration of anatomic architecture on close inspection: pitting edema	Readily apparent obscuration of anatomic architecture: obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL: gross deviation from normal anatomic contour	Progression to malignancy (i.e. lymphangiosarcoma): disabling	Death
Edema: viscera	Asymptomatic: clinical or radiographic findings only	Symptomatic: medical intervention indicated	Symptomatic and unable to ailment adequately orally: interventional radiology or operative intervention indicated	Life-threatening consequences	Death

2012 due to the global shortage of PLD but is now open to further enrollment. In TRINOVA-3 also known as ENGOT-Ov2 and Gynecologic Oncology Group-3001, trebananib is being combined with first-line carboplatin/paclitaxel for EOC, PPC, or FTC, followed by trebananib maintenance therapy for 18 months or until disease progression. The study was initiated in December of 2011, with final data collection for the primary endpoint of PFS expected in 2016. Importantly, all 3 of the phase III studies investigate trebananib at 15 mg/kg since increased exposure to trebananib was associated with improved clinical outcomes in the randomized phase II clinical trial where 10 mg/kg was used [11].

Side effect profile of trebananib

The AEs attributable to trebananib have been mild, reversible, and are distinct from side effects of other compounds that inhibit angiogenesis. Most of the ≥3 AEs have been hypokalemia and/or "edema". Paramount to the tracking of trebananib associated AEs, such as edema, is appropriate grading and prospective monitoring to determine the mitigating factors and natural history. Clinical trials to date have used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 to grade AEs [12] (Table 1A). The intent is to localize the effected part of the body and categorize the severity in the typical CTCAE v 3.0 fashion where grade 1 represents a mild AE, grade 2 a moderate AE, grade 3 a severe AE, grade 4 a life-threatening or disabling AE and grade 5 death related to an AE. In cancer patients, edema can impact a visceral organ or body cavity, such as pulmonary congestion, ascites, or pleural or pericardial effusion. As a trebananib associated effusion can cause an increase in CA125, measurement of this marker is not a reliable marker for progression of disease. Investigators should attempt to ascertain the etiology of edema, which may include, but is not limited to, tumor obstruction of lymphatic or blood vessels, congestive heart failure, iatrogenic fluid overload, renal insufficiency, nephrotic syndrome or other significant hypoalbuminemic states. As such, Amgen has simplified the reporting of edema in their late phase ovarian clinical trials (Table 1B).

Table 1B
Grading as proposed by Amgen in phase III trials of trebananib.

Edema/lymphedema should be classified and reported as:
- Localized (confined to a single body area, e.g. lower extremities only) or
- Generalized (contiguous extension to more than a single body area)

Additionally, both localized and generalized edema/lymphedema should be graded as follows:
- Grade 1 (mild): defined as trace thickening or faint discoloration of the affected area
- Grade 2 (moderate): defined as moderate thickening or marked discoloration; leathery skin texture; papillary formation
- Grade 3 (severe): defined as severe symptoms that may involve skin blistering or skin breakdown; limitations of activities of daily living (ADL)

As of March 2013, 7 published trials have reported the rates edema associated with trebananib among 536 subjects [4,5,13–17]. All focused on "peripheral edema" while 2 also reported on increased ascites formation. The rate of edema of any grade was 29% with 4% having grade 3 or 4 edema. Eight percent had grades 1 and 2 ascites (Table 2). It is not known if ovarian cancer patients treated with trebananib have a higher rate of edema compared to those with other solid tumors similarly treated. Other manifestations of edema such as those listed above have not been clearly elucidated. In addition, the natural history of trebananib associated edema is unknown. Importantly, in some of the placebo controlled trials, high rates of edema were seen even in the absence of trebananib. For example, in the placebo arm of the randomized phase II study using weekly paclitaxel in women with recurrent EOC, the rate of peripheral edema of any grade was 22% with 4% reporting > grade 3 edema while on the placebo arm [5]. Thus, all edema, even severe edema, is not necessarily caused by trebananib. Interestingly, the rate of edema of any grade in this ovarian study was 61%. Factors that might increase ones risk of trebananib associated edema are unknown and require further study.

Proposed mechanism of edema

Angiopoietins 1 and 2 are proteins binding to the Tie2 receptor, a cell-specific tyrosine-protein kinase located on both the vascular and

Table 2
Rates of edema associated with trebananib in unblinded clinical trials.

Author	Date	Study type	N	Peripheral edema (any grade)	Peripheral edema (grade 3/4)	Ascites (any grade)	Ascites (grade 3/4)
Herbst [4]	2009	Single agent—phase 1 (advanced solid tumors)	32	4 (13%)	0	1 (3%)	0
Doi [13]	2013	Single agent—phase 1 (advanced solid tumors)	18	7 (39%)	0	3 (17%)	0
Mita [14]	2010	Combination with chemotherapy—phase 1 (advanced solid tumors)	22	1 (17)	0	Unknown	Unknown
Rini [15]	2012	With sorafenib—phase 2 (kidney cancer)	101	34 (34%)	0	Unknown	Unknown
Karlan [5]	2012	With Paclitaxel—phase 2 (ovarian cancer)	105	64 (61%)	5 (5%)	Unknown	Unknown
Eatock [16]	2013	With cisplatin and capecitabine—phase 2 (gastro-esophageal cancer)	114	24 (21%)	1 (1%)	Unknown	Unknown
Peeters [17]	2013	With FOLFIRI (colorectal cancer)	144	19 (20%)	0	Unknown	Unknown
Total			536	153 (29%)	6 (4%)	4 (8%)	0

lymphatic endothelium. As such, angiopoietin 1 and 2 play an important role in angiogenesis and lymphangiogenesis, maintenance of blood vessel integrity and regulation of vascular permeability which are all crucial processes in tumor initiation, tumor growth, inflammatory pathways and metastasis processes [1,18,19]. Since trebananib binds and inactivates angiopoietins 1 and 2, the vascular permeability and the normal flow of the lymphatic and venous circulation can be perturbed, presumably leading to the accumulation of extracellular fluid in general and (lymph) edema specifically [1]. However, the exact pathophysiology is unknown and it is not clear if the edema is linked to decreased oncotic pressure, lymphatic vessel damage, leaky blood vessels, impaired venous return or peripheral vasoconstriction. As such, predisposing risk factors are unknown.

Diagnosis and monitoring of trebananib-associated edema

Repeated measuring of the circumference and volume of the lower extremities is often used as a monitoring tool for peripheral edema of the lower extremities (Fig. 1A and B). Interpretation of the measurements is made more difficult in cases of bilateral lymphedema in combination with change of the patient's body weight.

The edema in patients with EOC typically develops in the lower extremities during the first months of administering trebananib. In our experience the edema is reversible after stopping trebananib, but it usually takes 4 to 12 months to resolve. In addition, among some patients with clinically apparent edema developing after lymphadenectomy and administration of trebananib, the edema improves despite continuing the treatment with trebananib. The natural history of edema associated with trebananib is not clear. Therefore, patients require close monitoring as described above. Often the edema starts with a swelling on the forefoot that on palpation is pitting and occasionally evolves into a non-pitting, firm edema. Fig. 2 shows a typical case of edema one the dorsal forefoot, with an exceptional development of necrosis shown to be on pathologic examination due to vascular insufficiency. Notably, the necrosis disappeared within one month after stopping trebananib.

Management of edema during trebananib therapy

The management of trebananib associated edema is based on its anatomic location and severity. Clearly, discontinuation of trebananib is an integral part of treatment and should be done when ≥grade 3 swelling is noted. Dose reductions have not been studied as a

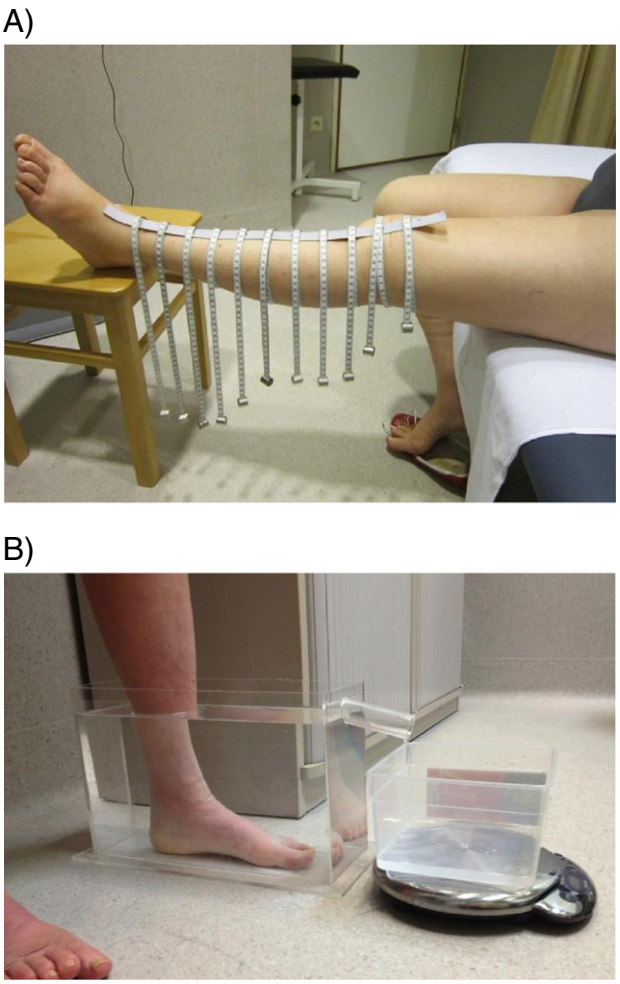

Fig. 1. A: Circumferences of both limbs are measured with a perimeter (with 4 cm intervals). B: The volumes of both feet and ankles are measured with a volumeter.

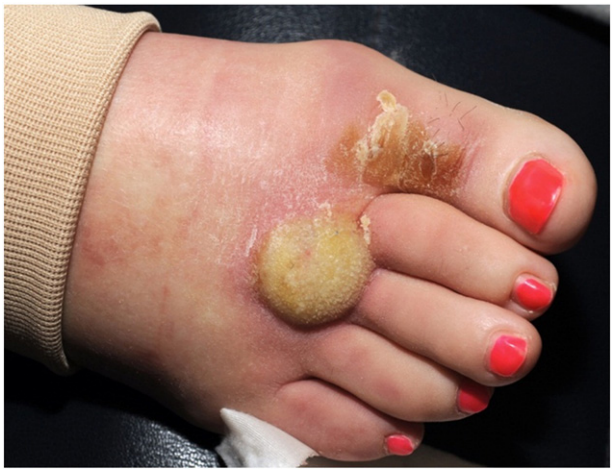

Fig. 2. Edema on the dorsal forefoot with development of a necrotic area in a patient with ovarian cancer treated with trebananib.

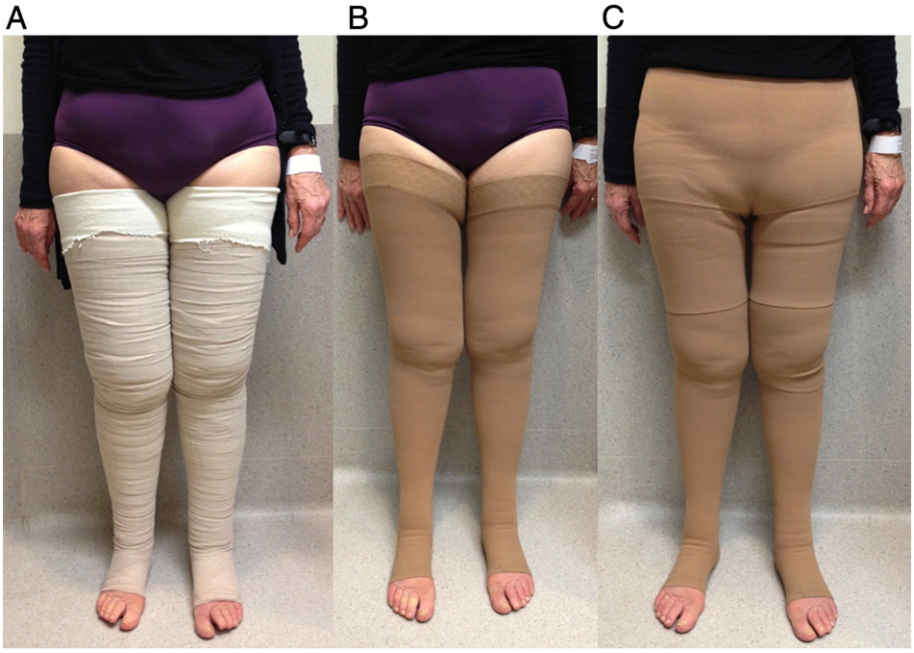

Fig. 3. A) Multi-layer bandage and B) garment for the legs with large stiffness, compression class III (34–46 mm Hg), mostly with open toe and C) for the pelvic region and belly, in a patient with edema during trebananib treatment.

therapeutic strategy because there does not appear to be a clear relationship to dose. Drainage of effusions can occasionally reduce symptoms but is generally avoided because of the associated reduction in serum protein levels and reduced oncotic pressure. "Institutional" guidelines have been developed in the University Hospitals of Leuven (Belgium) to treat peripheral edema attributable to trebananib (Table 3).

Conservative treatment is based on recommendations of the International Society of Lymphology [20]. According to these recommendations, lymphedema has to be treated with Decongestive Lymphatic Therapy (DLT) consisting of a two-stage treatment program. During the first or intensive phase, the lymphedema is treated daily during several weeks, until the lymphedema volume has been maximally reduced. This phase consists of skin care, multi-layer bandaging, exercises and manual lymph drainage. The second or maintenance phase aims to conserve and optimize the result obtained in the first phase. It consists of skin care, exercises, compression with an inelastic garment and manual lymphatic drainage when needed. Since the type of edema is usually multifactorial including lymphedema as well as venous stasis, the focus of the treatment has to be based on compression therapy (multilayer bandaging and garment wear) and exercise therapy [20,21]. This conservative approach can be combined with treatment with a loop diuretic such as furosemide. Importantly, patients being treated for grades 1 and 2 edema as described above should be watched very carefully for progression to grade 3 when discontinuation of trebananib is appropriate.

In Fig. 3, we show an example of a patient with A) a multi-layer bandage and B) an elastic garment to treat the edema of the legs and C) an additional elastic garment to treat the edema around the pelvic region and belly.

Conclusions

Edema associated with trebananib seems to be common; 29% on average among all studies but over 60% in ovarian cancer patients. Importantly, all edema associated with trebananib is not caused by trebananib as those receiving placebo also commonly report edema. Fortunately, trebananib associated edema is generally mild and rarely leads to drug discontinuation. Early treatment of edema is important and the edema is reversible. Risk factors and the natural history are as of yet unknown. It should be kept in mind that the edema is worst shortly after lymphadenectomy and improves with time in EOC patients treated with trebananib. Even mild edema can cause a burden for cancer patients and requires intervention. The presented guidelines for grading and management will hopefully lead to a better understanding of this idiosyncratic toxicity of trebananib.

Conflicts of interest

Drs. Bradley J. Monk and Beth Y. Karlan disclose that they received clinical research funding from Amgen for the AMG 386 trial. Other than this clinical research funding both doctors have no other conflicts of interest to disclose. Drs. Sandrina Lambrechts, Lindsey Minion, Nele Devoogdt, and Ignace B. Vergote have no conflicts of interest to disclose.

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Table 3
Institutional guidelines for the management of (lymph)edema associated with trebananib at the University Hospitals Leuven.

Modality	Purpose	Method
Conservative treatment		
Intensive phase of DLT	To decrease edema volume maximally	Start treatment early at the beginning of the development of edema. Treatment until stable edema-volume with skin care, multilayer bandaging, exercises and manual lymph drainage
Skin care	To improve or maintain skin condition To prevent skin injury and infection	Hydrate the skin daily before putting on the bandages Avoid wounds and disinfect wounds
Multilayer bandaging	To enhance lymph and blood flow under the bandage	Put the bandage from the feet up to the inguinal region (as high as possible) with a gradual decrease of the pressure
	To support the skin	The bandage consists of different layers: –an inner layer of tubular stockinet to protect the skin –padding to protect the joint flexures –padding with wavy structure in case of hard, fibrotic edema to create a massage-effect –compression with an outer layer of inelastic (short-stretch) bandages The pressure depends on the number of layers of bandages Teach the patient with edema to bandage herself Edema of the belly and pelvic region is treated with a custom-made cyclist pants A multilayer bandage is worn daily during 23 h a day and is only removed when the patient washes herself
Exercises	To enhance lymph and blood transport	Mobilizing exercises, such as walking, bicycling, but also local exercises such as tiptoeing and circumduction with the feet, while wearing the bandages Hydrotherapy Breathing exercises Exercise are performed 1 to 2 times a day during 10–30 min
Manual lymph drainage	To enhance lymph transport	Drain the region proximal of the bandage: empty the lymph nodes inside the belly, the iliac and inguinal lymph nodes and stimulate the development of anastomoses (for example between the inguinal and axillary lymph nodes) Manual lymph drainage is performed 3–5 times a week
Maintenance phase of DLT	To maintain the obtained edema reduction	Treatment with skin care, inelastic garment, exercises and manual lymph drainage
Skin care	See intensive phase	See intensive phase, but hydrate the skin after the garment is taken off (in the evening)
Inelastic garment	To enhance blood and lymph transport To protect the skin against wounds	Custom-made and measured by an experienced bandagist Garment for the leg: large stiffness, compression class III (34–46 mm Hg), mostly with open toe and with silicone board at the proximal end of the garment (to attach the garment distally to the inguinal region) In case of edema of the toes: toecap Garment for the pelvic region and belly: cyclist pants, compression class II (23–32 mm Hg)
Exercises	See intensive phase	See intensive phase, but while wearing the custom-made inelastic sleeve
Manual lymph drainage	See intensive phase	See intensive phase, but also draining the leg Frequency is decreased gradually to once a month
Intermittent pneumatic compression	To stimulate the resorption of water	The leg with edema is put in a boot that is inflated gradually from the ankle up to the inguinal region. Pneumatic compression may be applied daily during 30–45 min and additional to the intensive and maintenance phase of DLT
Limb elevation	To eliminate the gravitational force	Elevate the leg at regular time
Medical treatment		
Loop diuretic		
Furosemide	To increase diuresis by blocking the sodium potassium chloride transporter in the ascending loop of Henle	20 to 60 mg, 1 time a day

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