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Thalidomide (Thalomid) is recognized to have antiangiogenic properties and has been shown to be effective in the treatment of refractory myeloma.[1] As a result, thalidomide is now being investigated for use in a number of malignancies, including breast, lung, and renal cell carcinoma, as well as melanoma. The following is an account of a patient with two unrelated disorders (one malignant, one benign), both of which have responded to thalidomide.

Patient’s History

An active 77-year-old man in otherwise good health was referred to the surgical department in July 1996 because of a large, protuberant abdominal mass. The patient described a 1- to 2-year history of abdominal bloating and early satiety, and reported that the mass became larger following meals. In addition, he had lost 5 to 10 lb over the preceding 7 months. The patient also had a history of Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia), reporting nosebleeds every night as well as some rectal bleeding. His hematocrit typically ranged from the high 20s to low 30s. A prior computed tomography (CT) scan had shown cystic lesions in the liver. On physical examination, the patient had lesions consistent with this disease on his lips and tongue.

An abdominal ultrasound taken in June 1996 showed a 16-cm mass in the right upper quadrant, displacing the kidney and pancreas. The ultrasound was positive for ascites. A cystic mass was also discovered in the dome of the right upper lobe of the liver. A CT scan confirmed both masses (Figure 1). Fine-needle aspiration of the abdominal mass removed a large amount of bloody fluid, which, at the time, was negative for malignant cells. Aspiration reduced the size of the mass somewhat, but the mass did not resolve completely.

Series of Surgeries

In July 1996, the patient underwent surgery to remove the abdominal mass. Macroscopically, the tumor appeared to be highly vascular. The mass was purplish in color and was attached to one of the mesenteric arteries of the transverse colon. There were numerous satellite cystic lesions throughout the abdomen. Pathology revealed that the mass was a grade II epithelioid leiomyosarcoma, with 5 to 10 mitoses per high-powered field. All margins of all specimens, which included a portion of the omentum, were positive for tumor cells. Adjuvant chemotherapy was not recommended, based predominantly on concerns about tolerability.

The patient later developed nodules in the area of the abdominal incision. Following a CT scan, a second operation, performed in April 1998, removed the gall bladder and a portion of the diaphragm due to tumor involvement. Two additional operations were performed in September 1998 and June 1999 to remove progressive tumor growth. On each occasion, numerous small lesions (approximately 1 mm) were seen throughout the abdominal cavity. Following the final operation, the patient developed a pulmonary embolus that was mild but lengthened recovery time. This was treated by placement of a vena caval filter, as anticoagulation therapy was contraindicated.

Thalidomide Therapy Initiated

Due to the vascularity of the tumors, and in an attempt to circumvent the need for additional surgery, antiangiogenic therapy was considered. In August 1999, the patient was started on thalidomide, 250 mg/d. Adverse events reported by the patient included mild peripheral neuropathy in the fingers and toes, which, although mild, resulted in a dose reduction to 150 mg/d. The patient generally took the medication at night, and the mild sedative effects were not problematic.

In September 2000, the patient presented to the emergency room with complaints of abdominal pain. Surgery was again performed, and tumor was debulked. However, the numerous small lesions found during all previous surgical procedures were not observed. The few lesions present were well-formed, older lesions that had been present at the time of the previous operation, although they
appeared to be somewhat smaller in size. The patient currently has no symptoms, and is being followed closely. A CT scan confirmed shrinkage of existing lesions (Figure 2). Thus, the time between surgeries—initially every 6 to 8 months—has slowed considerably since thalidomide therapy was initiated. After this last surgery, the thalidomide dose was increased to 200 mg/d; the patient is tolerating it well.

**Benefits of Thalidomide Therapy**

Surprisingly, the patient’s symptoms related to Osler-Weber-Rendu disease have also diminished, in terms of both frequency and severity. The patient’s hematocrit has now stabilized in the low 40s, and nosebleeds occur less frequently. Before receiving thalidomide, the patient experienced three to four nosebleeds daily. With therapy, the frequency has been reduced to one nosebleed every 2 to 3 days. In addition, the nosebleeds are lighter and more easily stopped, lasting on average 1 to 2 minutes, as opposed to 45 to 90 minutes prior to thalidomide. Although these findings are anecdotal, it is intriguing to observe the antiangiogenic properties of thalidomide in a patient whose tumor is responding to this agent. Further investigation into the effects of thalidomide in solid malignancies as well as in certain vascular disorders such as Osler-Weber-Rendu disease certainly appears warranted.

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**Drs. Paul Richardson and Kenneth Anderson Respond**

The over-the-counter marketing of thalidomide in Europe during the late 1950s for the treatment of pregnancy-associated morning sickness was a tragic sentinel event in the history of drug development. As early as 1961, reports of teratogenicity and dysmelia (stunted limb growth) associated with thalidomide use prompted its subsequent withdrawal.[1,2]

The return of thalidomide as therapy for certain conditions stems from its broad array of pharmacoinmunologic effects.[3] This rehabilitation was reflected by its approval in 1998 by the Food and Drug Administration for the short-term treatment of cutaneous manifestations of moderate-to-severe erythema nodosum leprosum (ENL), together with its use as maintenance therapy to prevent and suppress cutaneous manifestations of ENL recurrence.[3] Thalidomide has since become the treatment of choice for ENL, and its wide spectrum of activity has fostered its application in a variety of disease states (Table 1).[3-5] Given its teratogenic effects, thalidomide is now used only under strict guidelines to ensure that no fetal exposure to the drug occurs.[4]

**Antiangiogenic Properties**

In the field of medical oncology, the discovery of thalidomide’s antiangiogenic properties coincided with the emerging importance of antiangiogenesis in tumor growth and progression. Thalidomide has proven to inhibit angiogenesis induced by beta-fibroblast growth factor in a rabbit cornea micropocket assay and by vascular endothelial growth factor (VEGF) in a murine model of corneal vascularization.[6,7]

In human studies, the drug appears to undergo activation to metabolites via antiangiogenic activity.[8] Given these antiangiogenic properties, thalidomide is currently being evaluated for the treatment of various solid tumors, multiple myeloma, and other hematologic malignancies.[9-13]

Results in multiple myeloma are particularly promising, although its precise mechanisms of action in this disease are not completely understood, and its antiangiogenic effects are believed to be only part of the means by which its antimyeloma activity occurs. These other potential actions include modulation of adhesion molecules, inhibition of tumor necrosis factor (TNF)-alpha, down-regulation of lymphocyte surface molecules, lowering of CD4-to-CD8 peripheral lymphocyte ratios, and direct effects on myeloma cells themselves.[10,14-18]

**Adverse Effects**

Sedation and constipation appear to be the most common adverse effects reported by cancer patients,[9,13,19] with peripheral neuropathy being the most serious adverse effect associated with thalidomide.[20] Use of this drug may also increase the incidence of thromboembolic events, although such events are rare when the drug is used as a single agent. However, recent reports have shown thromboembolic complications develop more frequently when thalidomide is combined with steroids and, in particular, with anthracycline-based chemotherapy. One study exploring a
combination of thalidomide with liposomal doxorubicin (Doxil) and dexamethasone was terminated prematurely due to thromboembolic complications.[21,22] The possible cardiovascular effects of thalidomide include bradycardia and hypotension. The risk of adverse cardiovascular events associated with thalidomide therapy appears to be greater when consumed together with multiple blood pressure-lowering medications by older patients with coronary disease.[20] It is well known that thalidomide must never be used during pregnancy, and recommended contraceptive practices must be followed by both men and women of childbearing potential.[4] The System for Thalidomide Education and Prescribing Safety (STEPS), implemented to ensure the safe distribution of thalidomide, requires that patients comply with contraception guidelines and mandatory surveillance procedures.[4] In addition, all health-care providers who plan to prescribe and/or dispense thalidomide must be registered with the program.[4]

**Case History**

In this context, the authors present an intriguing and informative case of a patient with abdominal epithelioid leiomyosarcoma and a prior history of Osler-Weber-Rendu disease. After initial diagnosis in 1996, the patient underwent repeated surgery for his truncal sarcoma until 1999 when, with widespread locoregionally recurrent disease, oral antiangiogenic therapy was pursued with thalidomide at a starting dose of 250 mg/d. Mild peripheral neuropathy prompted a dose reduction to 150 mg/d, but the drug was subsequently well tolerated, with a recent dose increase to 200 mg/d and treatment ongoing.

In terms of disease response, the widespread smaller vascular lesions previously seen at laparotomy reportedly disappeared, and the intervals between surgery have diminished. Moreover, the patient’s symptoms related to Osler-Weber-Rendu disease have markedly diminished, with reduced bleeding and a stable hematocrit.

**Mechanisms of Action**

D’Amato et al postulated that thalidomide acted as an antiangiogenic agent through the interruption of processes induced by beta-FGF and/or VEGF.[6,7,19] Moreover, in vitro studies suggested that the antiangiogenic effect of thalidomide was due to specific metabolites and not the parent compound.[23]

Another important property of thalidomide is that it selectively inhibits TNF-alpha production while leaving the immune system otherwise intact,[24] thus leading to its application in various disorders characterized by abnormal TNF-alpha activity. The exact mechanism of thalidomide-induced TNF-alpha inhibition is unclear, but it appears to be different from that of other TNF-alpha inhibitors such as pentoxyfylline (Trental) and dexamethasone.[25,26] One possible mechanism postulated by Moreira and colleagues is that thalidomide inhibits TNF-alpha synthesis by accelerating degradation of TNF-alpha messenger ribonucleic acid, resulting in significant although incomplete suppression of TNF-alpha protein production.[25,27]

Of particular interest is the recent demonstration that thalidomide decreases the binding activity of nuclear factor kappaB, which in turn controls activation of the TNF-alpha gene.[28] It has also been postulated that thalidomide’s effect on angiogenesis may be through TNF-alpha inhibition, because TNF-alpha has proangiogenic effects.[6] However, the absence of a demonstrable TNF-alpha effect in experimental models of angiogenesis, coupled with the inability of strong TNF-alpha inhibitors to directly influence angiogenesis, suggests that thalidomide’s antiangiogenic activity is not related to TNF-alpha inhibition alone.[6,7] Thus, the clinical effect on the vasculature described in this case is especially intriguing and is commensurate with thalidomide’s proposed mechanisms of action on new vessel formation and perhaps the down-regulation of cytokines such as TNF-alpha, which activate endothelium.

**Conclusions**

We would concur, therefore, with the author’s conclusions that studies of thalidomide in such vascular disorders and in angiogenesis-dependent tumors are warranted, with analysis of appropriate surrogate vascular markers to better define the mechanisms of action and efficacy in such specific disease settings.

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**References:**


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