

## Off-label use of thalidomide for the treatment of a bleeding cutaneous metastasis

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### ABSTRACT

We herein describe the case of a 65-year-old man with frequent hospitalizations for severe anemia due to several recurrent bleedings of a cutaneous metastasis of hepatocellular carcinoma, and its successful *off label* treatment with thalidomide therapy for controlling bleeding and reducing transfusion requirements.

### Case Report

A 65-year-old man was first admitted to our Division in July, 2013, for severe anemia [hemoglobin (Hb) level of 6.5 g/dL]. Family and personal anamnesis were uneventful, apart from a history of previous alcohol abuse.

In June, 2012, he was diagnosed as a carrier of multifocal hepatocellular carcinoma; the diagnosis was done on the basis of abdominal computed tomography (CT), elevate  $\alpha$ -fetoprotein serum levels and liver biopsy. The histological examination showed polygonal hepatocytes, displaying an eosinophilic granular cytoplasm, rounded nuclei and prominent nucleoli, with the presence of vascular invasion, the grade of differentiation was grade 3. The immunohistochemistry was positive for  $\alpha$ -fetoprotein and negative for cytokeratin 7 and 19. Hepatocellular carcinoma (HCC) staging at baseline was stage B ac-

ording to Barcelona-Clinic Liver Cancer classification. After oncologic evaluation he was then treated with sorafenib from September 2012 to July 2013.

Unfortunately the disease progressed and, at the time of admission to our Division, the patient showed lung, bone and skin metastases. In particular a huge metastasis (9x7 cm; Figure 1) of the breastbone body was actively bleeding and causing the anemia.

The patient was given tranexamic acid intravenously, locally medicated with pressure medication and submitted to transfusion with 5 units of packed red cells (PRC); he was dismissed with an Hb level of 11.0 g/dL.

During the following months he was admitted to our Division other four times (from July to December, 2013), always for severe anemia due to bleeding of the cutaneous metastasis. A total of 36 units of PRC were administered during that period. Figure 2 shows Hb levels at hospital admission, number of PRC administered and Hb levels at hospital discharge during these five hospitalizations.

He was also evaluated by a surgeon, in order to verify the feasibility of a surgical approach; this was eventually denied since the CT scan showed the neoplastic tissue/mass infiltrating the breastbone body and approaching the aortic arch (Figure 3).

During the last hospitalization, the off-label use of thalidomide was offered to the patient, in the hypothesis that the antiangiogenic effect of the drug could help to stop bleeding. Informed consensus was signed by patient.

On December 14, 2013, thalidomide, 100 mg daily, was started, without the association of any anti-thrombotic treatment. Ever since the metastasis did not bleed anymore and the patient maintained stable Hb levels around 9-9.5 g/dL.

He was followed as an outpatient with a blood test every two weeks for three months; during this period of time he did not experience any adverse effect of thalidomide in particular no thrombotic or hemor-

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rhagic adverse events. Eventually he died of neoplastic cachexia with no evidence of further bleeding.

## Discussion

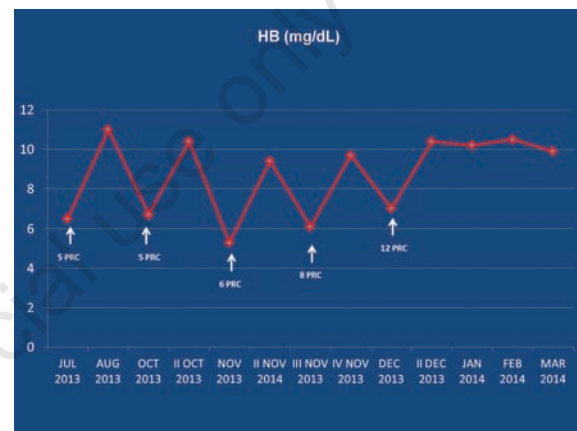
Thalidomide was first introduced in Europe in 1950s as a treatment for morning sickness, but was withdrawn early due to its severe teratogenic effects.<sup>1</sup> In the following years thalidomide, for its anti-inflammatory activity, was successfully used in the treatment of multiple diseases including multiple myeloma,<sup>2</sup> erythema nodosum,<sup>3</sup> Behçet's disease<sup>4</sup> and graft versus host disease.<sup>5</sup>

Thalidomide is even known because of some antiangiogenic effects, so that in the last few years it was used for therapy of recurrent gastrointestinal bleeding due to angiodysplasia<sup>6</sup> as well as refractory Crohn's disease.<sup>7</sup> No randomized trials are available but several case series have shown an interesting efficacy of thalidomide in reducing bleeding rate and in particular in reducing the need of blood transfusion in treated patients.<sup>6,7</sup>

The antiangiogenic effects of thalidomide seem to be related to a decrease in the synthesis of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor as suggested by *in vitro* and *in vivo* studies.<sup>7-9</sup>

Hepatocellular carcinoma is a highly vascularized tumor due to the process of angiogenesis and HCC angiogenesis has been identified as being critical for tumor growth and metastases. VEGF plays a crucial role in the development of metastases in HCC as suggested also in very recent studies,<sup>10</sup> so it seemed reasonable the *palliative-off label* use of thalidomide in this patient.

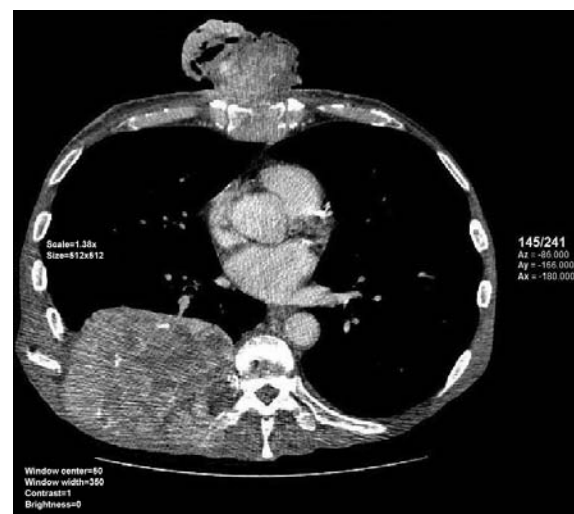
For the lack of randomized controlled trials the recommended dose to prevent bleeding is not established yet. Some Authors recommend a dosage of 300 mg/day, other 50-100 mg daily. Thalidomide has several side effects including; nausea, constipation, severe painful peripheral neuropathy, dizziness or lighthead-



**Figure 2.** Hemoglobin (Hb) levels at hospital admission, number of packed red cells (PRC) administered and Hb levels at hospital discharge during these five hospitalizations and during follow-up.



**Figure 1.** Picture of skin bleeding metastasis.



**Figure 3.** Computed tomography scan image in which is evident the skin metastasis.

edness, muscle weakness, anxiety and cough that seem to be dose dependent. Therefore to our opinion the starting dose of 50-100 mg/daily should be safer in minimizing the side effects of the drug.

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## Conclusions

To our knowledge this is the first report of thalidomide use to prevent recurrent bleeding in skin metastasis of HCC. Our results suggest a potential *off label* use of thalidomide in bleeding tumors or metastases in order to reduce transfusion requirements and hospitalization.

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