Thalidomide: a treatment option for bleeding GI angiodysplasias in dialysed patients

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Keywords: angiodysplasias; angiogenesis; dialysis; thalidomide

Introduction

Gastrointestinal (GIT) bleeding is a serious problem in dialysed patients, and can lead to repeated hospitalizations, invasive diagnostic and therapeutic procedures and the need for multiple blood transfusions. Angiodysplasias are the cause of GIT bleeding in 3–6% of all patients [1,2], and in the elderly population they constitute the most common cause for obscure GIT bleeding [3]. As early as 1984, angiodysplasias, often multiple and located throughout the GIT, have constituted a potential source of bleeding in dialysis patients [4].

Today, the ever-increasing use of the wireless capsule endoscope has dramatically improved our ability to accurately diagnose angiodysplasias ([1], Figure 1). Fortunately, many bleeding angiodysplasias stop bleeding spontaneously [2]. But, for those vascular malformations that continue to bleed or bleed recurrently, therapy remains unsatisfactory. Multiple lesions are the rule, rather than the exception. Therefore, surgical resection of any involved segment of the bowel is fraught with the uncertainty of other lesions bleeding at a future point in time. Argon laser coagulation is an accepted mode of therapy, but many angiodysplastic lesions, to be found in the distal small bowel, are ‘out of technical reach’ of this modality. Medical options have also disappointed, with uncertainty still existing over the use of estrogenic hormones in treating bleeding angiodysplasias [5].

Discussion

Angiodysplasias are arteriovenous vascular malformations located on the mucosal and submucosal surfaces of the GIT. Their pathogenesis is still not clear, and probably multifactorial. These malformations are thin-walled, fragile vessels. They bleed, often recurrently, and in such a severity, as to require blood transfusions. Vascular endothelial growth factor (VEGF) is an angiogenic peptide that is secreted in response to hypoxia, stimulates proliferation of vascular endothelial cells and increases vessel permeability [7]. GIT angiodysplasias are characterized by elevated serum levels of VEGF [8]. In addition, colonic angiodysplasias stain for both VEGF and basic fibroblast growth factor, another known angiogenic factor, and they also express the VEGF-receptor 1 along their endothelial lining [6]. If suppressing VEGF may lead to a disruption in the pathogenesis behind these pathological vessels, then the use of VEGF suppressive (antiangiogenic) agents may be useful in treating bleeding GIT angiodysplasia. Thalidomide is such a drug [9].

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mide led to a decreased size and number of angiodysplasias
sule endoscope showed that successful therapy with thalido-
levels [8]. Furthermore, the serial usage of the wireless cap-
also significantly reduced high pre-treatment serum VEGF
thalidomide treatment not only stopped GIT bleeding but
bleeding (Table 1; [1,8,13–15]). In three patients, low-dose
demonstrated thalidomide’ s ability to stop angiodysplastic
stop GIT bleeding [12]. Since then, a number of reports have
hypothesized that the anti-angiogenic effects of thalidomide
Crohn’ s disease is often unrelated to disease activity, it was
follow-up period [11]. As GIT bleeding in patients with
3 weeks, and bleeding did not recur during a 4-month
After starting thalidomide, all bleeding stopped within
∼ in 6 months and had required 40 blood transfusions.

Table 1. Patients’ summaries after thalidomide therapy for bleeding angiodysplasias

| References | Patient age/sex | Location of angiodysplasia | Blood transfusions | Thalidomide dose and duration of therapy | Immediate result of thalidomide therapy | Long-term results of thalidomide therapy |
|------------|-----------------|-----------------------------|--------------------|------------------------------------------|-----------------------------------------|----------------------------------------|
| [1]        | Three patients, 2 M, 1 F, mean age: 78 years | NA                           | ≥ 2 units/month (≥ 3 months) | 50–400 mg, 3–12 months | Two patients stopped bleeding after 2–12 weeks; one patient did not respond | Two patients did not rebleed for 6 months after thalidomide was stopped |
| [8]        | 54, M           | Small bowel                 | > 200 units (42 months) | 100 mg, stopped after 4 months | Bleeding stopped within 2 weeks | No bleeding for 33 months |
| [8]        | 69, F           | Small bowel                 | 12 units (12 months) | 100 mg, stopped after 4 months | Bleeding stopped within 2 weeks | No bleeding for 24 months |
| [8]        | 72, M           | Jejunum, ileum              | > 1 unit/month (14 months) | 100 mg, stopped after 4 months | Bleeding stopped within 2 weeks | No bleeding for 22 months |
| [13]       | 60, F<sup>a</sup> | Stomach, jejunum            | 8 units/week (8 months) | 100–200 mg, 3 months | Decreased blood transfusions (2 units/week) | Died after 3 months (as a result of leukaemia) |
| [14]       | 80, M           | Duodenum, jejunum           | 35 units (4 months) | 100 mg stopped after 11 months | Bleeding stopped within 1 week, no bleeding for 11 months | Thalidomide cessation led to further episodes of bleeding |
| [15]       | 54, M<sup>b</sup> | Stomach, small and large bowel | > 130 units (15 months) | 50–150 mg, 6 months | Bleeding stopped immediately | No bleeding for 6 months |

NA: not available.
<sup>a</sup>This patient had underlying acute myelogenous leukaemia.
<sup>b</sup>This patient had Von Willebrand’s disease.

The tragic, early history of thalidomide needs no reintro-
duction. But, today, thalidomide is an important drug in
the management of multiple myeloma and erythema no-
dosum leprosy. It possesses anti-inflammatory and anti-
angiogenic capabilities [10]. Indeed, D’Amato showed, in
an experimental model, that thalidomide is capable of in-
hibiting VEGF and basic fibroblast growth factor-mediated
angiogenesis directly [9]. In gastroenterology, thalidomide
was initially used as an anti-inflammatory drug in patients
with active Crohn’s disease [8,11]. It was quickly recog-
nized that thalidomide stopped GIT bleeding in these same
patients. Wettstein et al. treated a 55-year-old woman with
Crohn’s disease and recurrent rectal bleeding with thalido-
mide, after all other medical therapies had failed. Before
commencement of thalidomide this patient had bled in-
cessantly, had been hospitalized on 12 different occasions
in 6 months and had required ~ 40 blood transfusions.
After starting thalidomide, all bleeding stopped within
3 weeks, and bleeding did not recur during a 4-month
follow-up period [11]. As GIT bleeding in patients with
Crohn’s disease is often unrelated to disease activity, it was
hypothesized that the anti-angiogenic effects of thalidomide
may be the predominant mechanisms behind its ability to
stop GIT bleeding [12]. Since then, a number of reports have
demonstrated thalidomide’s ability to stop angiodysplastic
bleeding (Table 1; [1,8,13–15]). In three patients, low-dose
thalidomide treatment not only stopped GIT bleeding but
also significantly reduced high pre-treatment serum VEGF
levels [8]. Furthermore, the serial usage of the wireless cap-
sule endoscope showed that successful therapy with thalido-
mide led to a decreased size and number of angiodysplasias
[3].

In all the reports on thalidomide therapy for GIT bleed-
ing, not even one patient with chronic kidney disease has
been included. Also, in a prospective study to be conducted
by the Northport Veterans Affairs Medical Center, as to
the efficacy of thalidomide in bleeding angiodysplasias, an
exclusion criterion is renal failure [16]. But why? Undoubt-
edly, bleeding GIT angiodysplasias can lead to an increased
morbidity and mortality in dialysed patients. Secondly, the
only patients who should not use thalidomide are women
of child-bearing age, or sexually active men who are not
using condom contraception. Thirdly, Eriksson et al. have
shown that dose adjustment/reduction is not necessary in
patients with chronic renal disease or in haemodialysed pa-

<sup>a</sup>This patient had underlying acute myelogenous leukaemia.
<sup>b</sup>This patient had Von Willebrand’s disease.
of therapy, and serial electromyelograms appear warranted. Fortunately, peripheral neuropathy becomes overtly problematic only after high cumulative doses of thalidomide have been given [12].

Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, improved GIT bleeding in a patient with haemorrhagic hereditary telangiectasia [18]. However, reports of bowel perforation, following its use in patients with advanced ovarian cancer, means that, as of the moment, this drug cannot be recommended as therapy in angiodysplastic bleeding [19].

Conflict of interest statement. None declared.

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Received for publication: 1.5.08
Accepted in revised form: 19.5.08