Colorectal cancer: response to sunitinib in a heavily pretreated colorectal cancer patient

Joan Manel Gasent Blesa[a] and Enrique Grande Pulido[b]

A 64-year-old man was admitted to the emergency room in May 2000 due to pelvic pain, functional disability of the lower limb, and bleeding from a rectal fistula. The patient was diagnosed with a rectum-sigma adenocarcinoma (pT1N0M0 stage). After surgery by left hemicholectomy, the patient received adjuvant chemotherapy with tegafur for 6 months. Due to the development of subsequent recurrences (infravesical relapse, bone and lung progression) associated with CEA progression and pain worsening, the patient received treatment by every available agent for the metastatic colorectal cancer, including oxaliplatin and radiotherapy; irinotecan; FOLFOX schema; oral capecitabine; raltitrexed; irinotecan and cetuximab; cetuximab as a single agent; always in combination with zolendronic acid-based treatment for pain control. Once the patient had progressed to all the approved drugs available in the market, sunitinib (50 mg/day given for 4 weeks followed by 2 weeks of rest) was proposed as compassionate use. The patient received sunitinib for a total of 6 months (four cycles). On account of the nonmeasurable disease nature of the metastatic presentation in the present case, the clinical benefit was measured in terms of reduction of painkiller intake, improvement in performance status of the patient, and CEA serum levels. In addition to all of these clinical and biological data, CT images showed an increase in necrotic area of the bone lesion without any decrease in tumor size by classical RECIST criteria. The patient is still under sunitinib treatment and has recovered his normal daily activity. *Anti-Cancer Drugs* 21 (suppl 1):S23–S26 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2010, **21 (suppl 1):**S23–S26

Keywords: colon cancer, heavily pretreated patient, sunitinib

[a]Medical Oncology Department, Hospital Marina Alta Denia, Alicante and [b]Pfizer Spain Medical Department, Alcobendas, Madrid, Spain

Correspondence to Joan Manel Gasent Blesa, Hospital Marina Alta de Denia, Partida Plana Est, 4 03700 Dénia-Alicante, España
E-mail: JOANMAGASENT@telefonica.net

A 64-year-old man was admitted to the emergency room in May 2000 because of pelvic pain, functional disability of the lower limb, and bleeding from a rectal fistula. The patient was diagnosed with adenocarcinoma using a Rectum-Sigma pT1N0M0. After surgery by left hemicholectomy, the patient received adjuvant chemotherapy with tegafur for 6 months. In July 2003 he was diagnosed with a local infravesical relapse, and subsequently began chemotherapy treatment with oxaliplatin with concomitant radiotherapy until a total dose of 61.2 Gy was reached in November 2004.

In January 2004, bone progression (left ischiopubic branch) was detected, and the patient started treatment with irinotecan every 3 weeks until the completion of 10 cycles in August 2004 (Fig. 1). On account of uncontrolled pain and increase (from 11 to 14 ng/ml) in the serum levels of carcinoembrionary antigen (CEA), the patient started a new chemotherapy treatment with FOLFOX 4 scheme every 3 weeks completing 5 cycles by December 2004, with a CEA in the fourth cycle of 23.2 ng/ml.

In January 2005, the patient started a new-line treatment with oral capecitabine, for a total of nine cycles until August 2005, achieving a serum CEA stabilization (24.04 ng/ml). Radiotherapy in the left ischiopubic branch was required because of worsening pain and zoledronic acid-based treatment was then initiated, which continues until now.

Subsequently, new serum CEA progression was shown and the patient began treatment with irinotecan plus bevacizumab, completing a total of eight cycles until November 2005. Since January 2006, with a serum CEA of 212 56 ng/ml, the patient was treated with raltitrexed (5 mg) every 3 weeks. Since April 2006, and because of lung progression [PET/computed tomography (CT)], the patient started a weekly treatment with irinotecan–cetuximab, with toxicity resulting in grade 2 diarrhea and with a partial response by Response Evaluation Criteria In Solid Tumors (RECIST) criteria (CEA and CT). Consolidation radiotherapy was given for the lung lesion between November 2006 and January 2007, with a clinical complete response by RECIST criteria. Unfortunately, a new progression disease was detected in May 2007 (increase of CEA up to 64 ng/ml and radiographic progression of lung lesions by CT). Therefore, in July 2007 the patient started another new treatment with cetuximab given as a single agent in a weekly schedule. After an initial biochemical response, the patient finally failed to respond to the antiepidermal growth factor receptor (EGFR) treatment because of a new increase in CEA (68 ng/ml) and a new clinical/radiological worsening.

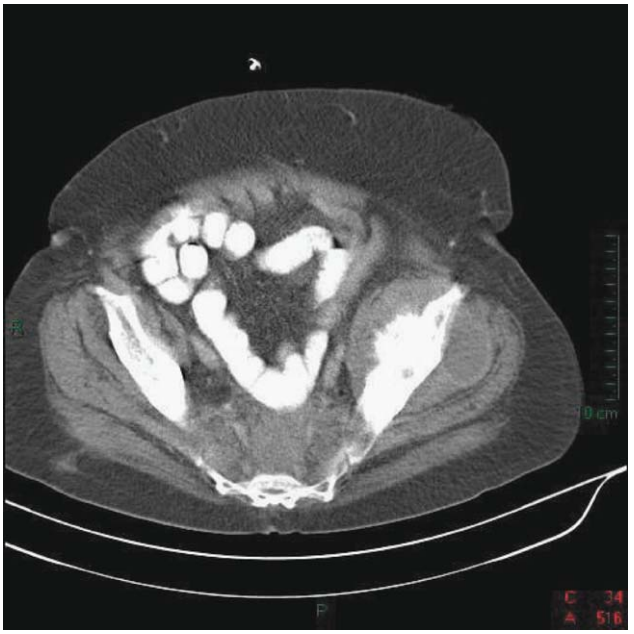
0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/01.cad.0000361533.36428.0b

Once the patient had progressed to all the approved drugs available in the market, sunitinib was proposed as compassionate use based on the data published by Saltz *et al.* [1]. The patient started treatment with sunitinib at the approved dose of 50 mg/day given for 4 weeks followed by 2 weeks of rest. The patient received sunitinib for a total of 6 months (four cycles), reaching a better performance status (from ECOG 2 down to 0), reducing painkiller intake, and experiencing continuous decrease in serum CEA levels during the treatment period (Fig. 2). In addition to all of these clinical and biological data, CT images showed an increase in the necrotic area of the bone lesion (Fig. 3) without any decrease in tumor size by classical RECIST criteria. The patient is still under sunitinib treatment and has recovered his normal daily activity.

Discussion

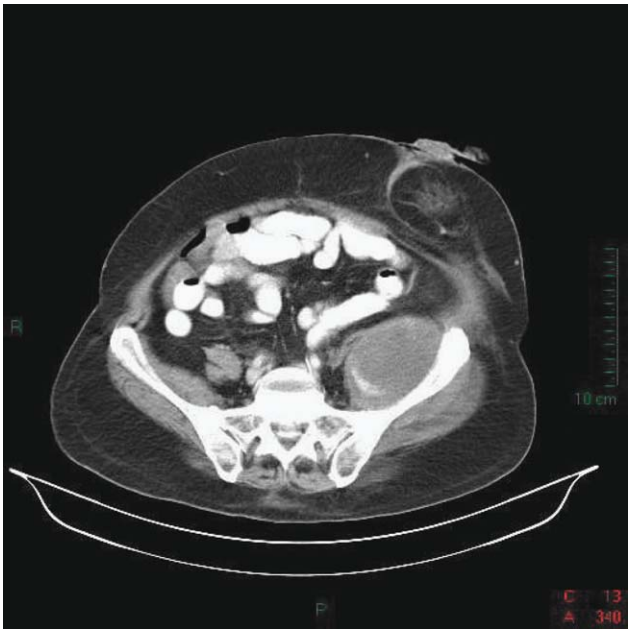
Colorectal cancer is the second most common cause of cancer deaths in the western world [2]. Despite the introduction in the last two decades of new chemotherapeutic agents that include fluoropirimidines, leucovorin, oxaliplatin, raltitrexed, irinotecan, and the more recent

Fig. 1



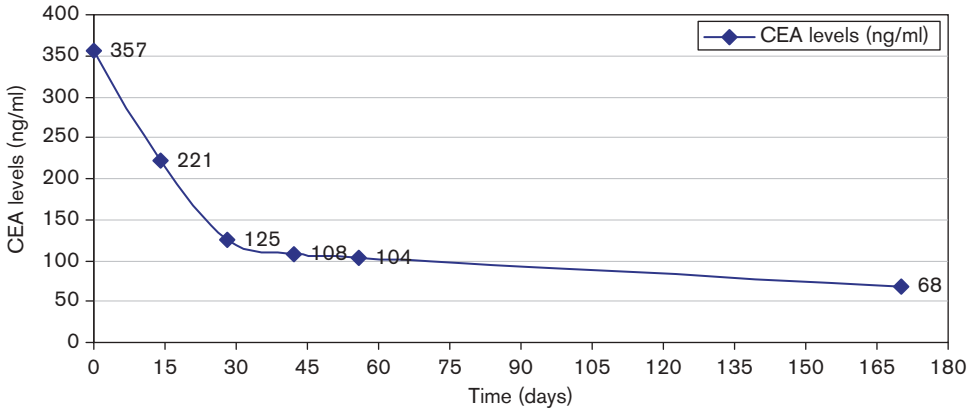
Computed tomography scan: left ischiopubic branch metastasis at diagnosis.

Fig. 3



Computed tomography scan: left ischiopubic branch metastasis after palliative radiotherapy and antiangiogenic treatment with sunitinib showing an increase in necrotic area inside the lesion but without any decrease in total size.

Fig. 2



Carcinoembrionary antigen (CEA) serum levels: evolution of CEA serum levels (ng/ml) in time after initiation of sunitinib treatment.

targeted-design agents, such as bevacizumab, cetuximab, and panitumumab, the life expectancy of newly diagnosed advanced colorectal cancer patients is no longer than 2 years [3]. Treatment of metastatic colorectal cancer is now considered a continuum of care in which what really impacts on clinical benefit is being able to give all the above agents at one point or another, irrespective of the use of the active agents singly or in combination [4]. Therefore, new treatment options that can be added to the current armamentarium are highly needed.

The treatment of colorectal cancer has dramatically changed in the last 15 years, not only in the metastatic but also in the adjuvant setting. In fact, it is estimated that approximately 40% of the patients who undergo potentially curative surgery will relapse at a distant location later during the course of their disease [5]. The introduction of new chemotherapeutic compounds, mainly irinotecan or oxaliplatin, has improved the response rates to treatment and overall survival in patients with advanced colorectal cancer [3]. Recently, new targeted agents directed against the EGFR, such as cetuximab or panitumumab, have shown that when added to standard chemotherapy they can improve overall response rates and prolong overall survival in patients with wild-type K-Ras [6].

The angiogenesis switch process is a key step in any solid tumor development. In colorectal cancer, the overexpression of the vascular endothelial growth factor (VEGF) has been associated with increased risk of recurrence, metastasis, and death [7]. There exist several strategies against this blood vessel formation; neutralizing monoclonal antibodies against VEGF and the VEGF receptors (VEGFR); small molecules that can block the tyrosine-kinase domain of the VEGFRs; and soluble VEGFRs [4]. Bevacizumab (Avastin, Genentech Inc., California, USA) is a humanized monoclonal antibody against the isoform-A of the soluble VEGF [8]. Bevacizumab was the first antiangiogenic drug in the market, and nowadays has shown an overall or disease-free survival advantage when added to standard chemotherapy for colorectal, breast, non-small-cell lung cancer, and renal cell carcinoma tumor types [9].

Despite all these newly available agents, the 5-year survival rate for metastatic colorectal cancer remains just 10% [10]. As of now, no preferred sequence of therapy has emerged and the choice of therapy is largely driven by the toxicity profile of the different agents. Moreover, patients, sooner or later, will relapse after treatment with all these new compounds because of resistance or intolerance to treatment. Therefore, there is a high unmet need to find new active agents to improve the prognosis of these patients.

Sunitinib malate (Sutent, Pfizer Inc., New York, USA) is an oral, multitargeted tyrosine kinase receptor inhibitor of the VEGFRs, platelet-derived growth factor receptors, stem cell factor receptor (c-KIT), glial cell-line derived neurotrophic factor receptor (RET), and FMS-like tyrosine kinase-3. Sunitinib is currently approved for the treatment of advanced renal cell clear cell carcinoma and for the treatment of advanced gastrointestinal stromal tumors after failure or intolerance to imatinib [11]. Sunitinib is a small molecule with a chemical structure similar to the ATP; hence it competes with the ATP for binding to the ATP domain of the intracellular portion of the tyrosine kinase membrane receptor. These new multitargeted molecules can inhibit angiogenesis in a more complete sense, not only by blocking all the VEGFRs known (1, 2, and 3), but also by blocking the pericyte platelet-derived growth factor receptors-β. Sunitinib can also directly inhibit the growth or survival of selected tumor types with dysregulated or overexpressed tyrosine kinase receptors involved in the regulation of cell proliferation or cell survival conferring to sunitinib a dual antiangiogenic and antitumor activity. Sunitinib has been shown to have activity in cell lines and xenograft models of colorectal cancer in the preclinical setting. In these preclinical colorectal models using HT-29 and Colo-205 cell lines, sunitinib has significantly inhibited tumor growth of established tumors, or even induced marked regression of largely established tumors [12,13].

Saltz *et al.* [1] carried out a proof-of-concept phase II trial with sunitinib given as single agent in 82 metastatic colorectal cancer patients who had failed to respond to standard therapy earlier. One patient achieved a confirmed partial response by RECIST criteria. The median overall survival time was 7.1 months in the earlier bevacizumab cohort and 10.2 months in the bevacizumab-naive cohort. The safety profile was similar to other studies with sunitinib in other tumor types. The adverse events reported most often were fatigue, diarrhea, nausea, vomiting, and anorexia. No treatment-related grade 4 events were reported in more than one patient.

The mild safety profile, the early clinical activity shown, and the easy administration management meant that sunitinib was started in several clinical trials in combination with standard chemotherapy such as FOLFOX, FOLFIRI, or capecitabine in the colorectal cancer setting.

In this case, a clear clinical benefit was observed in an earlier heavily pretreated patient with every available agent for metastatic colorectal cancer. Moreover, the patient received other palliative treatments such as radiotherapy and zoledronic acid for uncontrolled pain and bone disease. On account of the nonmeasurable nature of the metastatic presentation in this case, the clinical benefit was measured in terms of reduction of painkiller intake, improvement in performance status of the patient, and CEA serum levels. In the metastatic setting, there are no clear guidelines for CEA

follow-up, although continued monitoring in such patients is common in the oncology community [14]. A recent update on the value of serum CEA as a tumor marker in colorectal cancer has recently been published by the European Group on Tumor Markers. According to the European Group on Tumor Markers, the guidelines for using serum CEA as monitoring therapy in advanced disease is especially indicated in patients with nonevaluable disease using standard criteria and in combination with radiology imaging techniques [15].

On the basis of the promising early clinical data, we decided to request a compassionate use of sunitinib for this one patient who had failed to the respond earlier to all available drugs in the market. The patient received sunitinib for a total of 6 months, getting a better performance status (from ECOG 2 down to 0), a reduction in painkiller intake, and a clear decrease in serum CEA levels (Fig. 2). In addition to all of these clinical and biological data, CT images showed an increase in the necrotic area of the bone lesion (Fig. 3); however, no decrease in tumor size by classical RECIST criteria was observed.

Other multitargeted agents that are currently under development in colorectal cancer include sorafenib, vatalanib, ZD6474, and AMG706. The future use of these new compounds as single agents or in combination with chemotherapy will depend on prospective and randomized clinical trials that are currently ongoing.

Acknowledgements

Funding for the preparation of this manuscript was provided by Pfizer Spain. Medical writing assistance was provided by Sofia Perea, PhD on behalf of Wolters Kluwer Pharma Solutions. The authors have no conflicts of interest to declare.

References

1 Saltz LB, Rosen LS, Marshall JL, Belt RJ, Hurwitz HI, Eckhardt GS, *et al*. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol* 2007; **25**:4793–4799.
2 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer Statistics, 2007. *CA Cancer J Clin* 2007; **57**:43–66.
3 Reinacher-Schick A, Pohl M, Schmiegel W. Drug insight: antiangiogenic therapies for gastrointestinal cancers. Focus on monoclonal antibodies. *Gastroenterol Hepatol* 2008; **5**:250–267.
4 Cilley JC, Barfi K, Benson AB III, Mulcahy MF. Bevacizumab in the treatment of colorectal cancer. *Expert Opin Biol Ther* 2007; **7**:739–749.
5 Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. *Dis Colon Rectum* 1997; **40**:1–24.
6 Van Cutsen E, Oliveira J. Colon cancer: ESMO clinical recommendations for diagnosis, adjuvant treatment and follow-up. *Ann Oncol* 2008; **19** (**Suppl 2**):ii29–ii30.
7 Ishigami SI, Arii S, Furutami M. Predictive value of vascular endothelial growth factor (VEGF) in metastasis and prognosis of human colorectal cancer. *Br J Cancer* 1998; **78**:1379–1384.
8 Kramer I, Lipp HP. Bevacizumab, a humanized anti-angiogenic monoclonal antibody for the treatment of colorectal cancer. *J Clin Pharm Ther* 2007; **32**:1–14.
9 Pohl A, Zhang W, Ning Y, Manegold PC, Lurje G, Lenz HJ. Targeting metastatic colorectal cancer in 2008: a long way from 5-FU. *Oncology (Williston Park)* 2008; ;**22**:456–462.
10 Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics 2006. *CA Cancer J Clin* 2006; **56**:106–130.
11 Christensen JG. A preclinical review of sunitinib, a multitargeted receptor tyrosine kinase inhibitor with anti-angiogenic and antitumour activities. *Ann Oncol* 2007; **18** (**Suppl 10**):3–10.
12 Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, *et al*. *In vivo* antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003; **9**:327–337.
13 Marzola P, Degrassi A, Calderan L, Farace P, Nicolato E, Crescimanno C, *et al*. Early antiangiogenic activity of SU11248 evaluated *in vivo* by dynamic contrast-enhanced magnetic resonance imaging in an experimental model of colon carcinoma. *Clin Cancer res* 2005; **11**:5827–5832.
14 Fakih MG. CEA Monitoring in colorectal cancer. *Oncology* 2006; **20**:579–592.
15 Duffy MJ, Van Dalen A, Haglund G, Hansson L, Holinski-Feder E, Klapdor R, *et al*. Tumor markers in colorectal cancer: European Group on Tumor Markers (EGTM) guidelines for clinical use. *Eur J Cancer* 2007; **43**:1348–1360.