Combination of monoclonal antibody (Bevacizumab) and chemotherapy (FOLFIRI) in palliative treatment of metastatic adenocarcinoma of the small bowel (SBC): case report and review of the literature.

Rafał Stec[1], Bartłomiej Grala[2], Michał Mączewski[3], Lubomir Bodnar[1], Arkadiusz Zegadło[4], Cezary Szczylik[1]

[1]Department of Oncology, Military Institute of Health Services, Warsaw, Poland
[2]Department of Pathology, Military Institute of Health Services, Warsaw, Poland
[3]Department of Clinical Physiology, Medical Center of Postgraduate Education, Warsaw, Poland
[4]Department of Radiology, Military Institute of Health Services, Warsaw, Poland

Corresponding author:
Rafał Stec, MD
Department
of Oncology
Military Institute
of Health Services
128 Szaserów St.
00-909 Warsaw, Poland
Phone/fax: +48 22681 84 37
E-mail: drrafals@wp.pl

Submitted: 27 February 2009
Accepted: 15 April 2009

Arch Med Sci 2009; 5, 4: 647-651

Abstract

Small bowel cancer (SBC) is very rare malignancy. Annually about only 89 new cases of SBC are diagnosed in Poland (0.1-0.3%) of all malignancies and approximately 1% of gastrointestinal cancers. The prognosis of metastatic SBC is rather poor. The median survival of patients undergoing chemotherapy is approximately 14 months. Small bowel cancer is considered refractory to chemotherapy. Various anticancer agents have been tested in palliative chemotherapy of SBC: 5-Fluorouracil (5-FU), Cisplatin, Adriamycin, Mitomycin C, Oxaliplatin, Irinotecan, Carboplatin. Here we report a rare case of metastatic SBC with complete response (CR) after combination treatment with monoclonal antibody (Bevacizumab) and FOLFIRI (5-FU, Leukovorin, Irinotecan). The patient is alive without disease progression 28 months after her primary presentation of SBC.

Key words: small bowel cancer, chemotherapy, FOLFIRI, Bevacizumab.

Introduction

Small bowel cancer (SBC) is a very rare malignancy. Annually about only 89 new cases of SBC are diagnosed in Poland (0.1-0.3% of all malignancies and approximately 1% of gastrointestinal cancers). Small bowel cancer is the 54th most common malignancy in Poland [1, 2].

Risk factors of SBC include: familial adenomatous polyposis (FAP syndrome), hereditary nonpolyposis colorectal cancer (HNPCC syndrome), Peutz-Jegers syndrome, Crohn's disease, celiac sprue, neurofibromatosis type 1 [3]. Another potential the factors of SBC are mainly related to the diet and include: red meat as well as the preserved food in the diet [4].

Small number of SBC cases essentially precludes randomized, clinical trials that could establish optimal management of SBC at the stage of disseminated disease, i.e. whether and which palliative chemotherapy could be used in this setting.

Small bowel cancer is localized predominantly in the duodenum and jejunum (80%) [5]. The most common histological type of small bowel malignant tumors is adenocarcinoma (approximately 50% of cases), followed by neuroendocrine tumors (approximately 39%), and lymphomas,

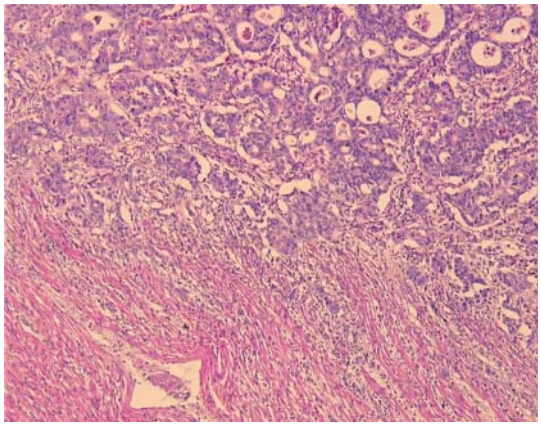

Figure 1. Infiltration of SBC in mucularis priopria. HE, 100×

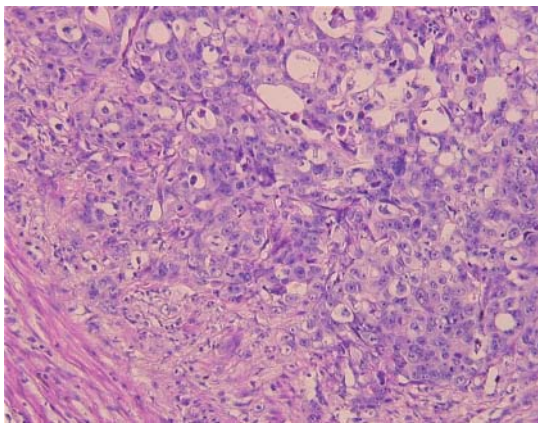

Figure 2. The deep invasive component of the tumour is closely related to the rete of slit-like, occasionally branching vascular channels, surrounding small nests of cancer cells HE, 200×

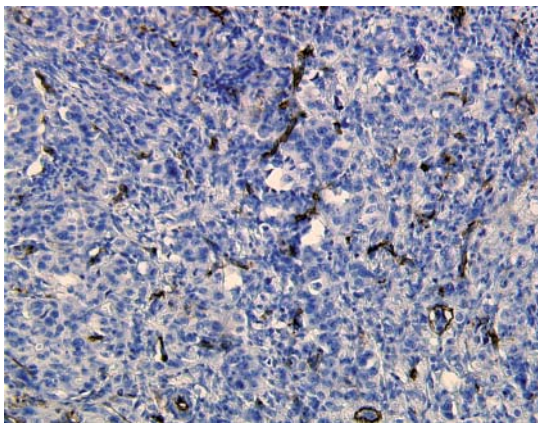

Figure 3. The same field with immunochemical reaction showing the presence of CD34 antigen, found in endothelium 200×

leiomysarcomas, gastrointestinal stromal tumors. Surgical treatment is the gold standard of therapy for small bowel malignant tumors (except for lymphomas). Chemotherapy has been attempted as a palliative treatment but its efficacy has been unsatisfactory (except for lymphomas) [6]. The most common chemotherapeutic regimens used in this setting are based on 5-FU, Leukovorin and Cisplatin [7].

Here we report a rare case of metastatic SBC with complete response (CR) to a combination treatment with Bevacizumab and FOLFIRI (5-Fu, Leucovorin, Irinotecan) and review literature of chemotherapy for SBC.

Case report

A 45-year old woman, had been admitted to Department of Surgery due to very potent abdominal pain on June 2006. Additional test were performed: abdominal ultrasound, gastroscopy and colonoscopy. Ultrasound demonstrated concrements in the gallbladder, up to 17 mm in diameter; gastroscopy demonstrated biliary reflux, colonoscopy – only II° hemorrhoids, apart from that the colon was normal. Ultimately the patient was diagnosed with cholelithiasis and was referred for an elective surgical intervention.

In July 2006 her abdominal pain returned and the patient was admitted to the hospital again. During hospitalization abdominal and pelvic computed tomography (CT) scan was performed and demonstrated enlarged mesenteric lymph nodes below the tail of the pancreas, with diameter ranging from 18 to 38 mm, enlarged small bowel loops to 54 mm in left epigastrium and hypogastrium with a narrowing of its lumen below described nodal changes, enlarged retroperitoneal lymph nodes with diameter ranging from 10 to 12 mm, the presence of a focal lesion in the liver in segment 6 with a diameter of 6 mm and calcified concrements in the gallbladder.

On 8 September 2006 the patient was operated due to subileus. A tumor of the jejunum was resected, cholecystectomy was carried out, and biopsy and termoablation of the liver metastasis (seg. 6) was performed.

In the pathological report:

- macroscopy: the 30 cm long fragment of small intestine with distinct presence of enlarged lymph nodes in mesentery and periintestinal fatty tissue; longitudinal dissection of the intestinal wall showed the solid tumor causing subtotal obstruction of the intestine, located 6 cm away from line of cut;
- histopathology: high (grade adenocarcinoma (adenocarcinoma tubulare partim carcinoma solidum G-3) with infiltration of total wall of small bowel and periintestinal adipose tissue (T3), multiple lymph nodes metastases (23/33 – N1) and liver metastases (metastases adenocarcinomatosae hepatis) (Figure 1);
- immunohistochemistry: strong positive reaction in CD 34 stain of delicate vascular channels in the deep invasive component of the primary tumor,

as a result of development of the rete of immature blood vessels (tumor angiogenesis) (Figures 2-5).

The pathological staging according to TNM scale was pT3N1M1 (liver) [8].

Then, the patient was admitted to Oncologycal Department Military Institute of Health Services in Warsaw for further treatment. After admission, a follow-up thoracic, abdominal and pelvic CT scan was performed. We found, mesenteric enlarged lymph nodes (up to 13 mm in diameter), a liver metastasis in segment 4 (Figure 6) (a lesion visible in CT in segment 6 of the liver was the lesion that underwent termoablation and it could not be classified as a target or non-target lesion) and right lung metastasis (segment 3). In October 2006, due to liver and lung metastases, the patient was qualified to undergo a palliative chemotherapy FOLFIRI (Irinotecan, 5-Fluorouracyl, Leukovorin) in adequate doses: 180 mg/m^2 on day 1; 400 mg/m^2 "bolus" on day 1 and 600 mg/m^2 on day 1,2; 200 mg/m^2 on day 1,2 combined with monoclonal antibody (bevacizumab) at a dose of dose 5 mg/m^2 on day 1. The treatment was approved by the appropriate local ethical committee. Before treatment a written consent was signed by the patient. After 3 months, in January 2007 (after 7 cycles of chemotherapy) the follow-up CT scan was performed. The liver metastasis was smaller (by about 60%) and no lung lesions were visible. This was classified as PR (partial response) according to RECIST criteria (Response Evaluation Criteria in Solid Tumors). The next follow-up CT scan was performed after 3 months in May 2007 (after 13 cycles of chemotherapy). We did not find any lesions. We obtained CR (complete response) (Figure 7) according to RECIST scale. We decided to terminate the treatment with monoclonal antibody and chemotherapy (FOLFIRI). After another 3 months, in September 2007 we confirmed CR by follow-up CT. The patient currently undergoes a follow up.

The toxicity of chemotherapy was acceptable: we observed only grade 1 leucopenia and grade 1 neutropenia according to CTC (Common Toxicity Criteria). During follow up period we plan to perform follow-up CT (thoracic, abdominal and pelvic) scans every 3-6 months over the first two years and then every 12 months until five years after the end of the treatment. The last CT scan was performed in December 2008.

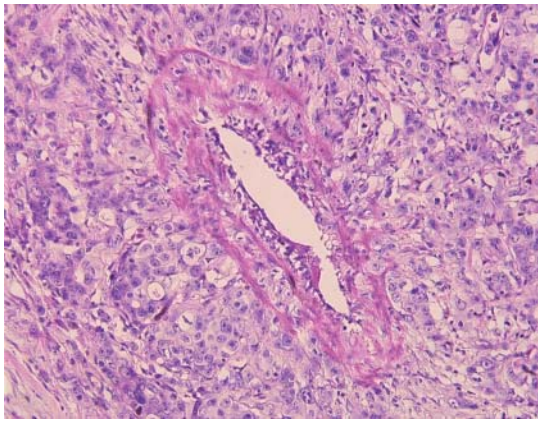

Figure 4. The invasive component of cancer forms evident angiocentric structures. The picture presents a medium-size vessel surrounded radially by compact strands of cancer cells. HE, 200×

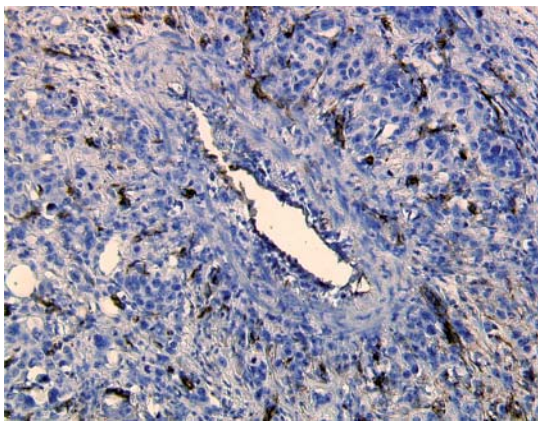

Figure 5. The above field with positive immunochemical reaction to CD 34. Radial arrangement of not only strands of the cancer cells, but also the rete of capillary vessels, is seen. 200×

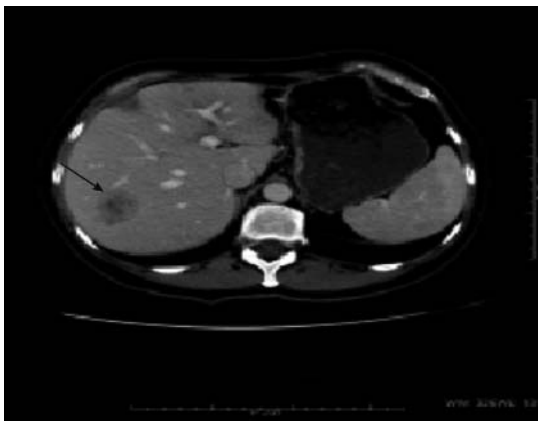

Figure 6. CT. Liver metastasis of SBC in segment 4 – post-operative and pre-chemotherapy

Discussion and review of the literature

Small bowel cancer is very rare malignant tumor, and thus it is very difficult to conduct a reliable, randomized clinical trial in this disease. Our experience comes from retrospective analysis and case reports.

Five year survival after radical, surgical treatment amount to 40-65% [5]. Median survival time for patients with metastatic disease, who underwent chemotherapy was 12 months, while it was only 2 months in the group of patients that received only symptomatic therapy [9].

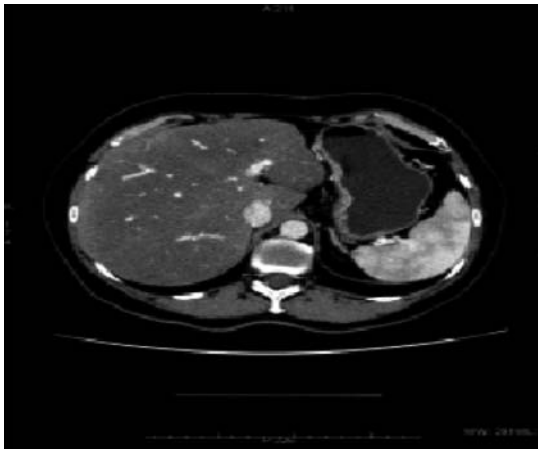

Figure 7. CT. Liver metastasis of SBC in segment 4 – post - chemotherapy. Complete remission

By analogy with colorectal cancer, adjuvant chemotherapy based on 5-Fu has been attempted in SBC, but no randomized phase III clinical trials support this management. Only various, non-randomized trials are available. These data are not sufficient to support the use of adjuvant therapy as a standard therapy for SBC despite its similar histology, biology and prognostic factors with colorectal cancer.

An analysis by MD Anderson Cancer Center of 59 patients with SBC, who received the adjuvant chemotherapy after radical surgical treatment, did not demonstrate improved of survivals. This could be a consequence of a small number of patients who received adjuvant treatment [9]. A retrospective analysis performed in Mayo Clinic demonstrated similar results: there was no improvement in survival associated with adjuvant chemotherapy [10]. Authors suggested that multicenter, randomizing clinical trials were warranted [5].

A few authors presented case reports from oncological centers where various regimens of palliative chemotherapy were used in SBC.

Cases of 14 with patients with advanced SBC, treated between 1950 and 1980 in the MD Anderson Hospital with palliative chemotherapy based on: 5-Fu, Adriamycin, Mitomycin C, nitrosourea compounds were analyzed. 9 patients obtained stable disease (SD), 2 patients – minor response and 1 – partial responses (PR), with median survival time 9 months [11].

All consecutive patients with SBC treated at Princess Margaret Hospital between 1986 and 2004 were indentified to the analysis. Data were registered 113 patients. 44 patients received chemotherapy (first or second line of treatment) based on 5-Fu, Gemcitabine, Irinotecan (36% had ORR – overall response rate, PR – 27%, CR – 9%). Higher ORR was obtained in patients, who received combination chemotherapy based on Gemcitabine or Irinotecan than in the patient, who received monotherapy with 5-Fu [12].

An analysis by Institute of Gustave Roussy included a 9-year period (1992-2000). Twenty patients with metastatic or unresectable SBC were treated chemotherapy based on: Oxaliplatin (3 patients), Carboplatin (2 patients), ECF regimen (Epirubicine, Cisplatin, 5-Fu – 2 patients), 5-Fu with Cisplatin (7 patients), 5-Fu, Leukovorin and Cisplatin (6 patients). Nineteen patients were evaluated. ORR was obtained in 21%, PR in 4 patients, minor response in 2 patients, SD in 9 patients, and the progression of disease occurred in 4. Threeteen patients received second line chemotherapy (8 patients FOLFIRI, 4 patients – 5-Fu, and one –

Table I. Responses of chemotherapy in metastatic SBC

Source (reference)	Anticancer agents	No. of patients trials	Objective response No. of patients	Median time of overall survival (95% CI) in months
M.D. Anderson Hospital [11]	5-Fluorouracil Adriamycin Mitomycin C compounds	14 (1950-1980)	CR – 0 PR – 1 + 2*	9 months (95% CI not reported)
Princess Margaret Hospital [12]	5-Fluorouracil Gemcitabine Irinotecan	44 (1985-2004)	CR – 4 PR – 12	28.5 (23.1 – not reached) after adjuvant chemotherapy 11.1 (8.9-22.0) months from the start of 1st regimen paliative chemotherapy
Institute of Gustave Roussy [13]	5-Fluorouracil Leucovorin Cisplatin Carboplatin Oxaliplatin Epirubicin	20 (1992-2000)	CR – 0 PR – 4 + 2*	4 months (95% 1 CI not reported)

**minor response – greater than 25% but less than 50% reduction of greatest perpendicular dimensions (stable disease in RECIST criteria), CI – confidence interval*

5-Fu, Leukovorin and Cisplatin). The median survival time was 14 months (5-36 months) (Table I) [13].

Angiogenesis is one of key elements of the tumor development. Briefly it involves proliferation the network of pathological blood vessels that supply the tumor with nutrients, support its growth, proliferation and ability to develop metastases. Markers of angiogenesis indicate that it is potentiated in the tumors. These markers include: VEGFR (vascular endothelial growth factor receptor), CD 31 (found mainly in mature blood vessel), CD 34 (found in the endothelium of immature blood vessel).

In our case, due to potent CD 34 positive reaction in the invasive component of SBC, we used a irinotecan-based regimen as the first line of palliative chemotherapy (due to similarity of colorectal cancer) in combination with antiangiogenic therapy (monoclonal antibody against VEGF – bevacizumab).

Mechanisms by which the bevacizumab is effective are based on: inhibition of the new vessel growth, regression of newly formed vasculature, normalization of tumor blood flow, increase the efficacy of cytotoxic agents, direct effects on tumor cells [14].

When CR was obtained, bevacizumab and chemotherapy (FOLFIRI) were discontinued. Combined treatment (monoclonal antibody and FOLFIRI) can be a highly active option of palliative treatment of SBC, with acceptable toxicity. Despite discontinuation of all therapies, OS (overall survival) in our patient exceeded 28 months. Now the patient entered the follow up phase.

Of course, multicenter, randomized, phase III clinical trials are required to support this hypothesis.

We have to bear in mind extreme diagnostic difficulties associated with SBC. No methods of early SBC detection are available (accidental, during other surgery or with an aid of "special intestinal capsule with a camera"). Indeed, the diagnosis was made in our patient at an advanced stage (when a liver lesion and subileus suggested possible malignancy), which was followed by therapeutic-diagnostic laparothomy.

Acknowledgments

Special thanks for Professor W. Kozlowski, The Head of Department of Pathomorphology, Military Institute of Health Services in Warsaw, for attentive site management.

References

1. Wojciechowska U, Didkowska J, Tarnowski W, Katoński W. Cancer in Poland in 2004. The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology. 2004 Chapter 12; 123.
2. Barclay TH, Schapira DV. Malignant tumors of the small intestine. Cancer 1983; 51: 878.
3. Green PH, Jabri B. Celiac disease and other precursors to small-bowel malignancy. Gastroenterol Clin North Am 2002; 31: 625-39.
4. Chow WH, Linet MS, Mclaughlin JK, Hsing AW, Chien HT, Blot WJ. Risk factors for small intestine cancer. Cancer Causes Control 1993; 4: 163-9.
5. Singhal N, Singhal D. Adjuvant chemotherapy for small intestine adenocarcinoma. Cochrane Database Syst Rev 2007; 3: CD005202.
6. Siedlecki P. Chemotherapy of Gastrointestinal Cancer. In: Cancer of digestive tract. Krawczyk M (ed.) [Polish]. PZWL, Warszawa 2001; 382.
7. Krzysztof G, Jeziorski A, Szawłowski W. Cancer of upper digestive tract and small bowel. In: Clinical oncology. Krzakowski M (ed.) [Polish]. Publishing house Borgis; Warszawa 2006; 866-7.
8. AJCC cancer staging handbook. Six edition. Small intestine 2002; 11: 119-23.
9. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of The small bowel. Presentation, prognostic factors and outcome of 217 patients. Cancer 2004; 101: 518-26.
10. Halfdanarson TR, Quevedo F, Mc Williams RR. Small bowel adenocarcinoma: A review of 491cases. J Clin Oncol 2006; 24: 4127.
11. Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. Cancer 1984; 53: 23-5.
12. Fishman PN, Pond GR, Moore MJ, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. Am J Clin Oncol 2006; 29: 225-31.
13. Locher CH, Malka D, Boige V, et al. Combination chemotherapy in advanced small bowel adenocarcinoma. Oncology 2005; 69: 290-4.
14. Ellis LM. Mechanisms of action of bevacizumab as a component of therapy for metastatic colorectal cancer. Semin Oncol 2006; 33 (5 Suppl 10): S1-7.