

Bevacizumab as Treatment for Chemotherapy-resistant Pancreatic Cancer

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Abstract. *A 74-year-old male, with refractory stage IV pancreatic cancer, was successfully treated with bevacizumab 5 mg/kg and combination chemotherapy consisting of gemcitabine, fluorouracil, leucovorin, irinotecan and cisplatin (GFLIP) every two weeks. The patient had rapidly failed initial treatment with GFLIP given in an identical dose and schedule. Large new liver lesions developed during active treatment. On adding bevacizumab to GFLIP, serial measures on CT confirmed an objective (RECIST) response. The tumor marker CA19-9 fell rapidly from 24,000 U/ml to less than 400 U/ml. This was accomplished with clinically inconsequential side-effects. This is the first demonstrated benefit of bevacizumab used in combination with previously failed chemotherapy for pancreatic cancer.*

Bevacizumab, an anti-VEGF antibody, has not previously been successfully combined with a failed-drug partner for the treatment of pancreatic cancer. For refractory colon cancer, it has improved both objective response rates and median survival when used in combination with a previously unused additional drug oxaliplatin. However, it has virtually consistently failed when used alone or in combination with a failed 5-fluorouracil regimen (1). Finding better partners for bevacizumab is essential for it to be even more effective in gastrointestinal cancers. The development priority is for the discovery and demonstration of drugs whose activity can be improved when used in combination with bevacizumab.

Bevacizumab has been only minimally tested in combination with chemotherapy for pancreatic cancer. A phase III trial of gemcitabine with and without bevacizumab is in progress in the CALGB. This trial is based on evaluation of primary therapy performed by University of

Chicago investigators. The updated phase II median survival time for patients was 9.0 months (2). Pancreatic cancer provides rich targets for inhibitors of angiogenesis, because neovascular growth is a prominent feature of some pancreatic tumors (3-5).

This laboratory and practice have developed several models for the successful use of ineffective and failed drugs with new drug partners. The demonstrated benefit of the combinations can clearly be attributed in significant part to the contribution of the "failed" drugs (6). This report describes the clinical application of an unpublished laboratory model which combined a "failed" cytotoxin with an inhibitor of angiogenesis. The latter was inactive when administered alone. Together they were synergistic, producing complete durable inhibition of the *in vivo* human tumor.

Case Report

A 75-year-old man had a technically successful Whipple resection in November 2003, following 1 month of painless jaundice. He relapsed rapidly within 6 weeks, with evidence of liver and lung metastasis on CT. He was treated unsuccessfully with low-dose GFLIP (gemcitabine 500 mg/m², irinotecan 80 mg/m², fluorouracil 400 mg/m² bolus followed by 1200 mg/m²/24-h infusion, leucovorin 300 mg/m² and cisplatin 40 mg/m²) from January 2004 to March 2004 for six cycles, using the sequential 24-h schedule. Failure was documented by evidence of large new liver lesions on CT imaging. Bevacizumab 5 mg/kg day 2 following cisplatin was added to low-dose GFLIP given in an identical dose and schedule. Baseline tumor marker levels consisted of CA 19-9 of 24,000 U/ml and CEA 27 ng/ml. CT of the abdomen showed liver metastases with three lesions greater than 1.5 cm.

In June 2004, after six cycles, the tumor markers significantly decreased (CA 19-9 2400 U/ml, CEA 4 ng/ml). In September 2004, after eleven cycles of chemotherapy with bevacizumab and GFLIP, CA 19-9 dropped to 350 U/ml and CEA to 3 ng/ml. Objective response was seen in the liver lesions, one lesion having completely resolved and the remaining two

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lesions decreasing to 0.8 and 0.6 cm in size, respectively. The patient remained clinically well and continued with no significant side-effects after nine months of treatment.

This fully informed patient was treated on an *ad hoc* basis. He had exhausted the conventional contemporary drugs and was not eligible for any easily available research option. He declined taxanes because of their side-effect profile. He was in excellent physiological condition, ideally meeting safety criteria for the drugs. He had no hypertension, proteinuria, cardiac compromise, coagulopathy, or bleeding. In theory, he had no special risk contradicting the addition of bevacizumab to GFLIP, given the low doses and prior wide margin of safety for the cytotoxins (7).

Discussion

This report describes the first instance of objective response of a refractory pancreatic cancer to bevacizumab. Additionally, some of the cytotoxic drugs were successful at lower dose intensity than reported to date in any successful combination with bevacizumab. The patient had previously failed all the drugs in the GFLIP regimen in identical doses and schedules. In combination with bevacizumab, the tolerance, safety and quality of life compared favorably to patients on standard chemotherapy.

The observed objective clinical success of bevacizumab in combination with a low-dose previously failed regimen suggests new clinical mechanisms of action and applications for bevacizumab. The mechanisms proposed for bevacizumab include its ability to improve the access of the drug to the tumor (8, 9). This could be especially beneficial when bevacizumab is used in combination with low-dose chemotherapy such as GFLIP.

The GFLIP regimen was developed based on a series of observations from our preclinical laboratory. It may be viewed as a potentially exceptional partner for further trials in combination with inhibitors of angiogenesis. It combines four classes of drugs that have been individually preclinically or clinically active in combination with inhibitors of angiogenesis (10-13). Intent-to-treat analysis of a large phase II experience found that GFLIP, as both a primary and secondary therapy, prolonged survival and produced frequent objective responses with no toxicities, in theory, limiting the use of bevacizumab. (7).

The low doses and every-two-weeks intermittent schedule, are reminiscent of the Folkman-proposed metronomic model in which cytotoxins exert their effect through inhibition of angiogenesis (14, 15). GFLIP also produces a high rate of stable disease and often slow but prolonged regression of tumors. This characteristic may in many theoretical ways complement, or benefit from, an inhibitor of angiogenesis (16, 17). Another mechanism of action is suggested by the profound fall in tumor markers in this and more than half the patients given GFLIP.

Tumor markers may fall without an objective response of the tumor, but, in theory, they may be surrogate measures of inhibition of other proto-oncogene tumor products, such as apocrine neovascular growth promoters

The effective combination of low-dose cytotoxic therapy with bevacizumab provides opportunities for further development of safe, yet complex, multidrug therapeutic strategies. Whether this patient's benefit was entirely attributable to bevacizumab alone is unknown, but unlikely. In drug development, single-agent application of bevacizumab is not well regarded by opinion leaders, given the improved objective response rate and the important examples of synergism observed when bevacizumab is used in combination with other antitumor agents (18, 19). It has very modest single-agent activity for the treatment of colon and breast cancer. To date, its only clinically outstanding activity as a single agent has been against renal cell carcinoma (20, 21). It has been abandoned as a single agent for tested gastrointestinal cancers, especially refractory cancers.

Post-Whipple-relapsed patients possibly benefit more from chemotherapy than conventional pancreatic cancer patients (17). Primary and Whipple-failed patients may be the best target group for new chemotherapy regimens. ESPAC has demonstrated that leucovorin/fluorouracil, considered ineffective for advanced pancreatic cancer, is effective when used as adjuvant therapy before relapse (22). This is perhaps the best evidence that the adjuvant group may offer special opportunities for the use of chemotherapy, even with otherwise ineffective drugs.

Recently, an interferon (INF)-containing high-risk intensive regimen has been described as a highly beneficial phase II adjuvant treatment after Whipple resection (23). Based on the observations described in this paper, INF could theoretically act as an inhibitor of angiogenesis through the mechanisms we postulated (24). However, there is no reason to limit the testing of bevacizumab to post resection patients, even if they are an ideal target group for investigational therapy. The patient described in this report was not typical of the ideal adjuvant-treated patient. The very rapid relapse, producing sizeable lesions and high tumor markers, is more characteristic of conventional stage IV patients.

Six additional pancreatic cancer patients, who had failed many prior drugs, were treated with bevacizumab added to individualized variants of the above combination chemotherapy regimen. This produced two additional objective responses, both continuing for more than six months with clinical benefit, and two brief minor responses with subjective benefit and with decrease in tumor markers. Two patients failed the described treatments entirely.

Formal testing of bevacizumab given with GFLIP (GFLIP-B) is warranted, avoiding patients with arterial thromboembolism, risks of bleeding, need for surgery, significant heart disease, hypertension and other prognostic

factors that predict an increase in the risks of side-effects due to either bevacizumab or chemotherapy. Pancreatic cancer is associated with the risk of bleeding due to collateral vessels, marginal ulcers, gastritis, tumor invasion and prior radiation, especially with progressive disease. Appropriate precautions can limit these potential complications to acceptable levels for treatment with bevacizumab as demonstrated in phase II trials. The future focus will be on the formal testing of GFLIP-B as primary medical therapy for patients with advanced pancreatic carcinoma. Moreover, it will include development of metronomic salvage regimens incorporating unused active promising drug partners for patients with chemotherapy-refractory tumors.

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