Description

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A). Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis. This policy examines the available evidence for the off-label use of bevacizumab in patients with advanced adenocarcinoma of the pancreas.

In the U.S., pancreatic adenocarcinoma is the tenth most common cancer in men and the fourth leading cause of cancer deaths in men and women. Only 7% of cases are detected at an early stage, and more than 90% of patients develop metastases. The 1-year survival rate is 25%; the 5-year survival rate is 6% overall, and 22% for those diagnosed early with only local disease. For patients with advanced, unresectable disease, the standard of care is gemcitabine. Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) as a single-agent first-line treatment for patients with locally advanced (stage II or stage III when surgery is not an option) or metastatic (stage IV) adenocarcinoma of the pancreas, including patients previously treated with 5-fluorouracil. Gemcitabine is sometimes given as part of combination therapy with another agent, such as erlotinib, which is approved by the FDA for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis, the growth of new vasculature. (1-4) Without angiogenesis, nutrients, oxygen and other essential molecules reach malignant cells only by passive diffusion from pre-existing blood vessels, which would limit most tumors to diameters of several millimeters. Certain normal physiologic processes (e.g., embryonic development, menstruation, wound healing) require angiogenesis, and some non-cancer pathologic processes are linked to angiogenesis (e.g., macular degeneration, atherosclerosis, psoriasis). (5)

Regulatory Status
Bevacizumab for the treatment of advanced pancreatic adenocarcinoma is not a U.S. Food and Drug Administration (FDA)-labeled indication.

Policy

Bevacizumab is considered investigational for treatment of advanced adenocarcinoma of the pancreas.

Policy Guidelines

The HCPCS code for bevacizumab is:
J9035: Injection, bevacizumab, 10 mg.

Rationale

This policy is adapted from a 2009 TEC Assessment. (6) The objective of the Assessment was to evaluate the use of bevacizumab in advanced adenocarcinoma of the pancreas to identify any incremental benefit of using bevacizumab in these patients, taking into account potential increases in survival and quality of life, as well as the effects of adverse events caused by the treatment. This policy has been updated annually, with the most recent MEDLINE literature search through August 2012.

Because vascular endothelial growth factor (VEGF) appears to play a role in pancreatic cancer, bevacizumab was considered a promising therapy, and the results of 2 Phase II trials seemed to indicate potential benefit as well. (7, 8) Approximately 89–93% of pancreatic cancer patients have a VEGF mutation, which is associated with early recurrence after surgery, liver metastases, and poor prognosis. Finding VEGF in tumors is also correlated with tumor size. (9)

Five studies were identified for review as part of the Assessment that tested the use of bevacizumab in patients with advanced adenocarcinoma. These studies consisted of 2 Phase III trials, 2 Phase II, and 1 Phase I trial. In all trials, bevacizumab was added to gemcitabine, the latter which is considered the current standard of care. Some trials also included other agents as well, including cisplatin and erlotinib.

The 2 Phase III studies, one by Kindler and colleagues (10) and the second by van Cutsem and colleagues, (11) provided the strongest evidence because of their design. Neither study demonstrated that the addition of bevacizumab resulted in a statistically significant difference in the primary outcome of overall survival (OS). For the secondary outcome of progression-free survival (PFS), the van Cutsem et al. study appeared to show benefit, while the Kindler et al. study did not.

Kindler and colleagues randomly assigned 590 patients with advanced cancer (local or metastatic) to gemcitabine with or without bevacizumab. (12) The trial was stopped early when it was determined that the combination of gemcitabine plus bevacizumab could not achieve longer survival than the gemcitabine-alone arm of the trial.

Van Cutsem and colleagues randomly assigned 607 patients with metastatic adenocarcinoma of the pancreas to gemcitabine plus erlotinib, with or without bevacizumab. (11) There was no
statistically significant difference between the 2 groups in the primary outcome of OS. The median OS was 7.1 months for the treatment group and 6.0 months for the control group (hazard ratio [HR]: 0.89; 95% confidence interval [CI]: 0.74–1.07%; p=0.21). The study reported a statistically significant difference in PFS of 4.6 months in the treatment arm and 3.6 months in the control group (HR: 0.73; 95% CI: 0.61–0.86%; p=0.0002). Although this secondary outcome was significant, there were few details given regarding the methods used to assess PFS, which may be subject to greater measurement error than OS.

It was anticipated that bevacizumab could offer benefit in advanced adenocarcinoma of the pancreas because the drug targets VEGF, which is thought to play an important role in pancreatic cancer and because of an apparently positive effect in a Phase II clinical trial. (12) Unfortunately, the results of 2 Phase III trials, one of which was stopped early because of lack of OS benefit, and the second recently released trial also showed no incremental benefit in OS.

In 2009, Crane and colleagues assessed 1-year survival in a case series of patients with locally-advanced, unresectable pancreatic cancer. (13) Overexpression of VEGF by pancreatic cancer cells may diminish the effectiveness of radiation therapy. The authors suggest that the action of bevacizumab in reducing VEGF expression may therefore improve radiation therapy outcomes. One-year OS in patients with locally-advanced disease receiving radiation and paclitaxel without VEGF inhibition was 43% in a previous study. To examine the effectiveness of the combination of bevacizumab, capecitabine, and radiation, 94 patients were recruited to detect a 15% improvement in the 1-year survival rate over the 43% seen in the previous study. Crane et al. reported a 47% survival rate (95% CI: 36% to 57%, not statistically different compared to the previous study). The authors concluded that the addition of bevacizumab does not contribute to an improved 1-year survival rate.

Javle and colleagues reported the results of a single-arm study of 50 patients with metastatic pancreatic cancer treated with capecitabine, gemcitabine, and bevacizumab. (14) The primary endpoint was PFS based on radiologic measure or tumor size, and serum CA 19-9 levels, the latter a biomarker associated with pancreatic cancer burden. Secondary endpoints included OS, response rate, and toxicity. In this study, discontinuation of therapy was higher than anticipated, with 46 of 50 (92%) subjects not continuing due to death, disease progression, or adverse events. Although some radiologic response and reduction in CA 19-9 levels did occur, PFS at 1 year was 19% (95% CI: 9.4-31.6%). Overall survival at 1 year reached 35.5% (95% CI: 21.7-49.5%). The authors commented that, based on this study and previous results for bevacizumab, they have chosen not to proceed with Phase III studies.

In 2010, Astsaturov and colleagues reported on a comparative trial for patients with metastatic pancreatic cancer. (15) Patients were randomly assigned to receive bevacizumab alone or in combination with docetaxel cytotoxic therapy. There was no blinding. The primary endpoint was PFS. However, at 4 months, only 2 and 3 patients were stable, respectively, and the trial was discontinued on the study-defined grounds of futility of less than 25% PFS at that time.

Ko and colleagues reported partial results of an observational study of gemcitabine refractory metastatic pancreatic cancer patients treated with bevacizumab and erlotinib. (16) Recruitment stalled after publication of the relative ineffectiveness of bevacizumab in the Phase III trials previously described. Of the 36 patients followed in the study, 8 reached the primary endpoint of 6-month survival (22%). This survival rate is inferior to published rates of cytotoxic regimens.
Martin and colleagues investigated the safety and efficacy of bevacizumab combined with gemcitabine followed by infusional 5-fluorouracil (5-FU) in patients with advanced pancreatic cancer in a Phase 2 trial. (17) The primary endpoint was the proportion of patients with PFS at 6 months from initiation of therapy. If PFS at 6 months was equal to or greater than 41%, the regimen would be considered promising. Of the 42 patients enrolled in the study, 39 were evaluable for the primary endpoint. PFS at 6 months was 49% (95% CI: 34% to 64%). Median PFS was 5.9 months (95% CI: 3.5 to 8.1), and median OS was 7.4 months (95% CI: 4.7 to 11.2). Partial response and stable disease occurred in 30% and 45% of patients, respectively. Grade 3 to 4 toxicities included fatigue (14%), hypertension (5%), and venous thrombosis (5%). The authors concluded that the study met its primary endpoint and that further investigation of anti-VEGF therapy in combination with fluoropyrimidine-based therapy is warranted in advanced pancreatic cancer.

Ko and colleagues conducted a Phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for advanced pancreatic adenocarcinoma. (18) Patients with locally advanced or metastatic pancreatic adenocarcinoma, previously untreated, were randomized to bevacizumab plus cetuximab, either with (Arm A; n=30) or without (Arm B; n=31) gemcitabine. Tumor assessments were performed every 8 weeks. The primary study endpoint was progression-free survival (PFS). The median treatment duration was 9 weeks in Arm A and 8 weeks in Arm B (range: 2.0-40.4). Patients in Arm A had median PFS and overall survival (OS) values of 3.55 months and 5.41 months, respectively, compared to 1.91 months and 4.17 months in Arm B. The study closed early due to lack of sufficient efficacy in both treatment arms. The authors concluded that the combination of cetuximab and bevacizumab did not result in promising activity with or without gemcitabine, and suggested that a strategy of dual epidermal growth factor receptor (EGFR)/VEGF inhibition in pancreatic cancer does not warrant further development.

Fogelman and colleagues conducted a Phase II trial of bevacizumab plus gemcitabine and oxaliplatin as first-line therapy for metastatic or locally advanced pancreatic cancer. (19) Eligible patients had stage III (n=14) or IV (n=36) pancreatic cancer and had received no prior gemcitabine. Treatment cycles were repeated every 2 weeks, and CT imaging was performed every 6 weeks. Fifty patients were enrolled: 14 had stage III disease, the remainder, stage IV. Median age was 59 years. The overall response rate was 36%; 34% demonstrated stable disease. The median PFS was 4.9 months; median survival was 11.9 months; 1 year survival was 42%. Patients with locally advanced disease lived 12.8 months; patients with metastatic disease lived 10.2 months. The authors concluded that the regimen did not meet the objective of a 14-month median survival and that the toxicity was significant.

Summary

Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not an FDA-approved indication. The available evidence does not clearly demonstrate that addition of bevacizumab to chemotherapy regimens for advanced adenocarcinoma of the pancreas improves the net health outcome of those patients. Therefore, bevacizumab for patients with advanced adenocarcinoma of the pancreas is considered investigational.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN) guidelines state that gemcitabine is recommended for pancreatic cancer patients with locally advanced or metastatic disease, and
studies have suggested some benefit from adding another chemotherapy agent (such as cisplatin or fluoropyrimidine). The guidelines state that the only new targeted drug for which there is evidence of a statistically significant increase in survival when combined with gemcitabine is erlotinib. (20)

**National Cancer Institute’s Clinical Trial Database**

No Phase 3 trials on the use of bevacizumab in advanced pancreatic cancer were identified.

**Medicare National Coverage**

No national coverage determination.

**References:**


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96413</td>
<td>Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug</td>
</tr>
<tr>
<td></td>
<td>96415</td>
<td>each additional hour (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J9035</td>
<td>Injection, bevacizumab, 10 mg</td>
</tr>
<tr>
<td>ICD-10-CM (effective 10/1/13)</td>
<td>C25.0 – C25.9</td>
<td>Malignant neoplasm of pancreas code range</td>
</tr>
<tr>
<td></td>
<td>3E03305, 3E04305,</td>
<td>Administration, physiological systems and</td>
</tr>
</tbody>
</table>

FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth
| 3E05305, 3E06305 | anatomical regions, introduction, percutaneous, antineoplastic, other antineoplastic, code by anatomical route (peripheral vein, central vein, peripheral artery, central artery) |

**Index**

Avastin, Pancreas Cancer
Bevacizumab, Pancreas Cancer