The Effects of Bevacizumab on Vascular Endothelial Growth Factor Blockade

Mekayla Korpinen

San Diego High School

Abstract
Colorectal cancer (CRC) is the fourth most common type of cancer and the second most common cause of cancer deaths in America. Recently the combination of Bevacizumab and chemotherapy has been found to be very effective in treating CRC. Bevacizumab, also known as Avastin, is a recombinant humanized monoclonal antibody that is used to blockade VEGF. Vascular endothelial growth factor (VEGF) is a protein that is known to promote angiogenesis (a process that maintains the balance between blood vessel growth and the needs of cells) by stimulating new vessel growth and directing the growth of already existing vessels. As tumors develop, they recruit blood vessels to continue their spread. VEGF is present the whole time working and supporting the vessels within the tumor causing it to grow larger and advance in stage. In a phase 3 study involving 220 centers in 15 countries, 820 patients 18 years or older with tumors that were not surgically removable, had cancer confirmed after examination of tissue under a microscope, had spreading colorectal cancer whose tumors had continued to grow up to 3 months after ending first-line treatment were treated with randomly assigned second-line chemotherapy with or without Bevacizumab. The combination of Bevacizumab and chemotherapy showed a 63% stabilization of the disease compared to only a 50% stabilization with chemotherapy alone. The Bevacizumab treatments also lead to increased long term survival and decreased tumor growth rates compared to the chemotherapy alone.

Background
The risk of developing colorectal cancer in your lifetime is 1/20 (5%). It is more common in men over the age of 50 although it can develop before this age. Of all the ethnic groups in the world, Jews of Eastern European descent have the highest risk of colorectal cancer. Smoking, heavy alcohol consumption, lack of physical activity, type 2 diabetes, and genetic mutations greatly increase the risk of developing this disease. The most common gene mutation linked to colorectal cancer is called L1307K APC which is found in 6% of the American Jew population.

Materials and Methods
The 820 patients selected were all 18 years or older, with tumors that were not surgically removable, had cancer confirmed after examination of tissue under a microscope, had experienced previous treatment with Bevacizumab in combination with first-line chemotherapy fluoropyrimidine plus oxaliplatin or irinotecan, and had a tumor disease according to RECIST (Response Evaluation Criteria in Solid Tumors). Each patient was assigned randomly through the second-order minimization algorithm of Pocock and Simon. This algorithm is a form of stratified randomization used to balance groups based on certain characteristics such as gender and disease severity. Participants were selected based on whether the patient had irinotecan-based vs. oxaliplatin-based first-line chemotherapy, lacked tumor growth or spread first line of treatment for greater than or less than 9 months, and time sense last Bevacizumab dose. Based on the characteristics listed above, patients were put into two groups, with the first group of 409 receiving Bevacizumab and chemotherapy and the second group of 412 patients receiving chemotherapy alone. Up to 28 days before the start of the study, tumor measurements were taken in each patient. These measurements were taken with a conventional or spiral CT, MRI, or radiography and were conducted every 8-9 weeks during treatment, until progressive disease.

Results
Patients who completed treatment or stopped treatment before tumor progression received follow up exams every 3 months for any necessary anticancer treatment, survival data, and reports of side effects. Tumor status was evaluated in those who stopped treatment until the tumor began to progress again. Continuously throughout the study, the patients side effects were noted but special attention was given before and after each treatment cycle. Patients treated with Bevacizumab were followed and closely monitored until their tumors no longer progressed or they passed away. Dose reduction was not allowed in either of the groups until the level of toxicity from treatment was determined to be too high. Only then were the doses changed for that specific patient. Once the dose was changed, it was not allowed to be returned to the original amount.

Conclusions
Compared to chemotherapy alone, long term survival and progression-free survival rates have been greatly improved due to the continued use of Bevacizumab beyond tumor growth. The combination of chemotherapy and Bevacizumab is very effective because it is used against the tumor after chemotherapy then the Bevacizumab is still there to block angiogenesis pathways and if Bevacizumab resistance occurs and alternative angiogenesis pathways are developing then the chemotherapy is there to destroy the excess cells. A question that had been raised about unacceptable toxicity risk and the continuation of Bevacizumab after disease progression. This study indicates that there was very little difference in toxicity between the groups. The continuation of a biological agent continues to help the patient without the possibility of additional toxicities associated with the initiation of a new agent.

Application to Biotechnology
Although Eastern Europeans of Jewish descent have the highest risk of developing colorectal cancer, it has been found that African Americans are the ethnic group that experience the most incidences and fatalities. In order to correct the inconsistencies of racial pinpointing, positive findings of these collaborative works not only apply to African Americans but to all colorectal cancer patients. This will help to improve rates of overall survival and progression-free survival.

Acknowledgements
I am extremely thankful to Dr. Ericka, Dr. Saunders, Dr. Chang, Ms. Darcy, Mrs. Winter, and Sheridan for taking time out of their summer to pour their wisdom into my life.

References

The data in figures 2 and 3 was collected from February 1, 2006 to June 9, 2010. The average amount of time for the Bevacizumab group without tumor growth was 5-7 months versus 1-4 months in the chemotherapy only group. Long term survival was an average of 9-23 months for Bevacizumab group and 5-22 months for the chemotherapy group. A stable disease was established in 253 (63%) patients and partial responses took place in 212(5%) of Bevacizumab patients versus 204(50%) and 14(3%) in chemotherapy patients. Negative side effects happened in 403 or 99% of the chemotherapy alone group and in 394 or 98% of Bevacizumab patients. The most common side effects, also known as adverse events, were diarrhea, physical weakness, lack of energy and low levels of white blood cells. Compared to chemotherapy alone the bevacizumab and chemotherapy combination had more occurrences of blood, bleeding, and gastrointestinal perforation. During this study’s time frame 11 patients passed away, 5 deaths were determined “not treatment related”, 4 occurred in the Bevacizumab group and 3 occurred in the chemotherapy alone group. There is no evidence supporting that a patients sex increases or decreases their treatment’s efficiency in anyway.

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