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Will the Addition of Oxaliplatin to 5-Fluorouracil (5FU), and Leucovorin Improve Disease Free Survival of Patients With Stage III Colon Cancer Who Had Surgical Resection of the Tumor?

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Will the addition of oxaliplatin to 5-fluorouracil (5FU), and leucovorin improve disease free survival of patients with stage III colon cancer who had surgical resection of the tumor?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not the addition of oxaliplatin to 5FU and leucovorin will improve disease free survival of patients with stage III colon cancer who had surgical resection of the tumor.

Study Design: Review of three published, double blind randomized control trials in the English language in 2004, 2007, and 2009.

Outcomes Measured: The outcome is disease free survival of colon cancer. It is measured using periodic patient follow-up. History and PE, neuro assessment, liver and kidney function tests, CEA test, CBC, and imaging studies such as colonoscopy or barium enema are some of the assessments done at follow-up.

Results: All three articles used found similar results in that oxaliplatin is effective when added to 5FU and leucovorin. The first study has an average follow-up of 42.5 months and a disease free survival of three years. The numbers needed to treat (NNT) was twenty-four. The number need to harm (NNH) was ten for all three of the articles. The second article had an average follow-up of 81.9 months and a five year disease free survival. The NNT was seventeen. The last article used had an average follow up at 37.9 months and a disease free survival of three years. The NNT was nineteen.

Conclusions: The addition of oxaliplatin to 5-fluorouracil (5FU), and leucovorin does improve disease free survival of patients with stage III colon cancer who had surgical resection of the tumor.

Key Words: colon cancer, colorectal cancer, oxaliplatin, eloxatin

INTRODUCTION

Colon cancer refers to a primary cancer of the large intestine. Most are adenocarcinomas meaning they result from epithelial cells. The process begins when an adenomatous polyp undergoes malignant transformation. Increased size of a polyp and the presence and degree of dysplasia correlate with potential for malignant transformation. Because this process is so slow, risk increases with age. Approximately ninety percent of patients with colon cancer are over the age of fifty. About four percent of patients diagnosed with colon cancer are under the age of forty and those are typically hereditary types.[1] This type of cancer is very common in the United States, most likely due to diet. However, incidence has decreased in the United States over the last ten years because of the increased use of screening tools, including colonoscopy. Other common areas to find colon cancer include Europe, Australia and New Zealand. It is uncommon in India, South America, and third world countries.[1] Although the exact cause of colon cancer is unknown, risk factors include high-fat and low-fiber diet, age, and family history. Diseases such as inflammatory bowel disease (Crohn's Disease and Ulcerative Colitis), Gardner Syndrome, Familial Adenomatous Polyposis (FAP), and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) or Lynch Syndrome also increase the risk for developing colon cancer.[1]

This cancer is extremely relevant to patients and PA practice because it is currently the second leading cause of cancer related mortality. Fortunately, mortality has decreased in the United States over the last twenty years, and the five-year survival has increased. This is due to the development of newer drugs and different multimodality therapy. The most important prognostic indicator is the stage of the cancer. The stage depends on how deep the tumor has spread into the wall of the colon and the number of lymph nodes involved.[2] The cost of colorectal cancer in the United States is approximately fourteen billion dollars annually. Colorectal cancer ranks second as far as highest cancer related costs, behind only breast cancer. It is also projected that the total cost of all cancers could reach up to $158 billion dollars annually

by 2020 in the United States.[3] It is unknown how many healthcare visits are dedicated to colon cancer each year in the United States; however, it is estimated that less than sixty percent of patients over the age of fifty that are recommended to be screened are actually tested.[3]

Signs and symptoms associated with colon cancer are dependent on the location of the tumor. Right sided tumors typically cause fewer symptoms because the stool is not yet formed. Left sided tumors are more common and typically cause more symptoms because the stool is formed and the colon is narrower. Some signs and symptoms include, but are not limited to fatigue, weakness, weight loss, colicky abdominal pain, shortness of breath, bleeding, melena, change in bowel habits (diarrhea, constipation, and change in consistency or stool caliber), hematochezia, or tenesmus.

Treatment of colon cancer depends on staging. Surgical resection is the treatment of choice unless contraindicated. Both laparoscopic and open surgical resections have similar outcomes and rates of recurrence.[1] Additional options include radiation and chemotherapy. With stage III colon cancer, surgical resection followed by chemotherapy is the preferred method. Approximately forty to fifty percent of patients that do not receive adjuvant therapy after potentially curative surgical resection will relapse and die of metastatic disease.[2] Chemotherapy agents used include fluorouracil (5FU) and leucovorin with or without oxaliplatin. The reason the addition of oxaliplatin is being proposed is a higher rate of disease free survival at five years was reported when used with 5FU and leucovorin as opposed to using 5FU and leucovorin alone. This was found to be true in patients treated within six months postoperatively.[3]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not the addition of oxaliplatin to 5FU and leucovorin will improve disease free survival of patients with stage III colon cancer who had surgical resection of the tumor.

METHODS

The population studied includes patients with stage III colon cancer who had surgical resection of the tumor, while the intervention is oxaliplatin. The comparison is the effectiveness in the treatment of colon cancer with 5FU and leucovorin versus the addition of oxaliplatin therapy to 5FU and leucovorin. The outcome will be disease free survival of colon cancer and the studies used include three double blind randomized control trials.

The key words used in searches were "colon cancer," "colorectal cancer," "oxaliplatin," and "eloxatin." All articles were published in the English language. The articles were searched via Medline and Pubmed. Cochrane Systematic Reviews was also searched to rule out any previous systematic reviews on the topic. Articles were selected based on relevance and whether they included patient oriented outcomes (POEMS). The inclusion criteria included randomized control trials within fifteen years while exclusion criteria included patients without prior surgical resection, stage I or IV colon cancer, history of colon cancer or other cancers requiring invasive chemotherapy or other therapy. The statistics reported or used were p-values, NNT, and NNH.

OUTCOMES MEASURED

The outcome is disease free survival of colon cancer. It is measured using periodic patient follow-up. History and PE, neuro assessment, liver, and kidney function tests, CEA test, CBC, and imaging studies such as colonoscopy or barium enema are some of the assessments done at follow-up.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Andre, 2004 (1)	RCT	2246	18-75	• Stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) colon cancer • History of complete resection • Age 18-75 years • Inferior pole of the tumor above the peritoneal reflection (at least 15cm from anal margin) • Karnofsky performance-status score of at least 60 • CEA <10ng/mL • Adequate blood counts and liver and kidney function	• History of prior chemotherapy, immunotherapy, or radiotherapy • Treatment >7 weeks after surgery	46	FL alone (5FU + leucovorin) vs. FL with oxaliplatin
Andre 2009 (2)	RCT	2246	18-75	• Stage II (T3 or T4, N0, M0) or stage III (any T, N1 or N2, M0) colon cancer • History of complete resection • Age 18-75 years	• Prior chemotherapy, immunotherapy, or radiation • Treatment >7 weeks after surgery	27	FOLFOX4 (5FU, Leucovorin, oxaliplatin) vs. LV5FU2 (5FU + leucovorin)
O'Connell 2007 (3)	RCT	2492	Divided by <60, 60-64, and ≥65	• Patients with stage II (T3-4, N0, M0) or stage III (T1-4, N1-2, M0(colon cancer, • History of surgical resection of the tumor, • No evidence of residual malignant disease within 42 days of random assignment • Distal end of tumor ≥12cm from anal verge • Adequate hematologic, renal and hepatic function	• Clinically significant peripheral neuropathy (grade 2 or higher) • Other medical conditions that preclude chemotherapy administration • History of colon cancer or other invasive cancers • Laparoscopic colectomy unless patient was enrolled in one of two phase III clinical trials evaluating efficacy of laparoscopic colon resection	85	FULV (5-FU and leucovorin) vs. FLOX (5FU, leucovorin, and oxaliplatin)

RESULTS

The three randomized control trials in this systematic review compared the use of oxaliplatin with 5FU and leucovorin to using 5FU and leucovorin alone in the treatment of stage III colon cancer after surgical resection. The study by O'Connell observed 2,492 patients, but only 2,407 were eligible. The group receiving 5FU and leucovorin only (FULV) had 1,245 patients while the group receiving 5FU with leucovorin and oxaliplatin (FLOX) contained 1,247 patients. There were fifty-eight patients considered ineligible due to exclusion criteria. Twenty-seven had no follow-up data and twenty-five of them were due to consent withdrawal. The data for those twenty-seven individuals was not included in the analysis. Of the patients without follow-up and the group considered ineligible, thirty-eight were in the FULV group and forty-even were in the FLOX group. The patients were monitored on average for 42.5 months. The number need to treat (NNT) and number needed to harm (NNH) were calculated using absolute benefit increase (ABI) and absolute risk increase (ARI) respectively. Table 2 and 3 show the results. NNT was twenty-four meaning twenty-four patients would need to be treated for one more patient to benefit from this treatment when compared to control. The NNH was ten meaning only ten patients would need to be treated with this particular therapy in order for one more to be harmed by the potential side effects when compared to control.[4]

Of the 2,407 patients, 677 failed treatment due to recurrence, second primary disease, or death without recurrence. Sixteen percent of the total number of patients had died by the time analysis was done five years after the last patient started. In the FULV arm this included 198 patients while the FLOX group contained 187 patients. At four years, the disease free survival for the FULV group was 67.0% while the FLOX group was 73.2%. Also calculated was the relapse-free interval. After four years, the FULV group was 72.9% while the FLOX group was 78.1%.[4]

The study by Andre in 2009 monitored 2,246 patients with 1,123 in each of the two treatment groups. The average time for follow-up was 81.9 months. Each group was scheduled to receive twelve cycles of chemotherapy. Of the patients in the FULV group 74.7% received the treatment while 86.5% of patients in the FLOX group received the treatment. The average dose of oxaliplatin was 810mg/m^2. The patients that did not receive therapy were considered ineligible based on exclusion criteria. The NNT and NNH are shown in tables 2 and 3 below. The calculated NNT was seventeen meaning in order for one more patient to benefit from the use of oxaliplatin compared to 5FU and leucovorin alone, seventeen patients must be treated than when compared to control. The NNH was ten meaning one more patient would be harmed by the side effects of the treatment for every ten patients treated compared to control.[2]

The chance of surviving stage III colon cancer six years after the follow-up was 68.7% for the FULV group and 72.9% for the FLOX group. This results in a twenty percent decrease in risk of death in the FLOX group compared to the FULV group. Disease free survival at five years was 58.9% for the FULV group and 66.4% for the FLOX group. There were a total of 283 deaths (25.2%) in the FULV group and 245 deaths (21.8%) in the FLOX group mostly due to relapse and recurrence; however, twelve total deaths were due to adverse events, six from each group.[2]

The study by Andre in 2004 observed 2246 patients with an average follow-up of 37.9 months. Each group contained 1123 patients. Of the 1123, 1108 were deemed eligible in the FLOX group while 1111 were able to receive FULV. The forty-one patients not included were ineligible based on the inclusion and exclusion criteria for the baseline disease. Of the eligible patients, 74.7% in the FULV group received all the cycles of chemotherapy while 86.5% of patients in the FLOX group received all the cycles. The NNT and NNH were calculated in this study as well. The results are also in table 2 and 3 below. The calculated NNT was nineteen

meaning one more patient would benefit from the addition of oxaliplatin to 5FU and leucovorin for every nineteen patients treated compared to control. The NNH was ten meaning for every ten patients treated with oxaliplatin, one more will be effected by an adverse reaction.[5]

Analysis was done at follow-up (average 37.9 months). At that time 21.2% of patients in the FLOX group had relapsed or died compared to 26.1% of patients in the FULV group. After calculating the hazard ration (HR), this results in a 23% decrease in risk of relapse in the FLOX group. The disease free survival chance for the FLOX group was 78.2% compared to 72.9% in the FULV group.[5]

All three of the randomized control trials included CI and p-values. These are reviewed in table 2 below. The CI was 95% for all three and the p-values were <0.004, 0.003, and 0.002 in study one, two, and three respectively.[2,4,5]

Table 2

	Control Event Rate (CER)	Experimental Event Rate (EER)	Absolute Benefit Increase (ABI)	Numbers needed to treat (NNT)	CI	p-value
O'Connell[4], 2007	0.72	0.76	0.04	24	95%	<0.004
André[2], 2009	0.67	0.73	0.06	17	95%	0.003
Andre[5], 2004	0.73	0.78	0.05	19	95%	0.002

Table 3

	Control Event Rate (CER)	Experimental Event Rate (EER)	Absolute Risk Increase (ARI)	NNH
O'Connell[6], 2007	0.10	0.20	0.10	10
André[5], 2009	0.02	0.13	0.11	10
Andre[4], 2004	0.02	0.12	0.10	10

Each article reviewed the safety and tolerability of oxaliplatin and reported the severity of the side effects based on grade. Grade three and four were considered the most severe. These findings are in Table 4. The study by Andre in 2004 reported 92.1% of patients treated with

oxaliplatin had peripheral neuropathy. This was compared to the group treated with only leucovorin and 5FU in which 0.2% of patients reported peripheral neuropathy. Of the 92.1% of patients treated with oxaliplatin and complaining of peripheral neuropathy, 50% had grade one symptoms and 12.4% reported severe or grade three symptoms. One year after completion of treatment with oxaliplatin, only 1.1% of patients still had grade three neuropathy while 70.5% reported grade 0 meaning no change or no symptoms.[5] Other common grade three and four adverse events were neutropenia, diarrhea, and vomiting. All side effects were reported more common and more severe, or more likely to be grade three or four, in the group receiving oxaliplatin.[2,4,5] In the 2004 study by Andre, 56.3% of patients treated with oxaliplatin reported any grade of diarrhea while 48.4% of patients treated with leucovorin and 5FU only had diarrhea. Vomiting was reported in 47.2% of patients treated with oxaliplatin and only 24% of patients not receiving the addition of oxaliplatin. Neutropenia was found in 78.9% of patients receiving oxaliplatin and 39.9% of those that did not.[5] The same trend was true for all other side effects studied.

Table 4

Adverse Event (any grade)	Oxaliplatin + Leucovorin and 5FU	Leucovorin + 5FU
Peripheral Neuropathy	92.1%	0.2%
Diarrhea	56.3%	48.4%
Vomiting	47.2%	24%
Neutropenia	78.4%	39.9%

DISCUSSION

This systematic review investigated three RCTs for the effectiveness of using oxaliplatin in addition to 5FU and leucovorin as opposed to using 5FU and leucovorin alone in the treatment of surgically resected stage III colon cancer. Although each of the studies used a different disease free survival time frame, ranging from three years to five years, they all ended with similar results. Using oxaliplatin in addition to 5FU and leucovorin as adjuvant therapy in the treatment

of colon cancer is better than using 5FU and leucovorin alone. There were no specific or obvious outliers in any of the articles used.

The studies are all limited by sample size. Each article used over 1,000 patients, however; as mentioned previously colon cancer is the second leading cause of cancer related mortality in the United States. It is estimated that there will be 136,830 new cases and 50,310 colorectal cancer related deaths in 2014.[3] Studying a larger sample will be more beneficial for future use of oxaliplatin. Another limitation was that all three studies included stage II colon cancer in addition to stage III.

Oxaliplatin is an antineoplastic agent that works by preventing growth of cancer cells. By stopping the growth, the cells will eventually die. It is given intravenously over two hours at the same time as leucovorin, and 5FU is given after administration of the other drugs. This combination is typically given every other week. The Food and Drug Administration (FDA) approved the use of oxaliplatin in 2002. Generic forms have been approved, but are not as readily available currently. Other uses of oxaliplatin include other types of cancers, especially metastatic colorectal cancer, gastric carcinoma, and metastatic pancreatic adenocarcinoma. Contraindications of its use include allergies to the drug and pregnancy or breast-feeding. Oxaliplatin may cause birth defects even if it is the male being treated at time of conception. Caution should also be used if the patient plans to have children in the future due to the possibility of sterility. Kidney disease, liver disease and hepatitis, heart disease, CHF, diabetes, gout, and infection are not contraindications to using oxaliplatin; however, special consideration should be given to the drug frequency, dosage, or timing. Patients should avoid ice and cold drinks around the time of oxaliplatin administration. There is also a risk of bleeding when oxaliplatin is used with other medications that affect blood clotting. Examples include Vitamin E, NSAIDs, warfarin, ticlopidine, or clopidogrel.[6]

When comparing NNT and NNH, the decision to use oxaliplatin becomes complicated. Each of the three studies found that the NNH was lower than the NNT, meaning more patients would be harmed by the drug than successfully treated. The recommendation is still that oxaliplatin should be used because the potential side effects described in the results are worth the risk. Although some side effects are deadly, most were mild. Also, the majority of patients no longer had symptoms one year after completing treatment, as discussed in the results. Most of the patients that still had peripheral neuropathy after completing treatment are able to lead normal lives, especially with the help of medications like gabapentin.

CONCLUSION

The addition of oxaliplatin to 5-fluorouracil (5FU), and leucovorin does improve disease-free survival of patients with stage III colon cancer who had surgical resection of the tumor. All three studies found similar results in that oxaliplatin is an effective treatment because it is able to improve disease free survival and mortality rates. It should be recommended in patients with stage III colon cancer after the surgical resection of the tumor. Future research needs to focus on the side effects of using oxaliplatin. The articles mentioned that the NNH was lower than the NNT, but still recommended use of the drug because of its improvement of disease free survival. More research needs to be done on this and the long-term effects of patients living with mild, moderate, and severe adverse events. Further research could also include more information on stage II vs. stage III colon cancer regarding the use of oxaliplatin.

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