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Is Necitumumab an effective addition to traditional chemotherapeutic regiments when treating stage IV lung and colon cancer?

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A SELECTIE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirement for the Degree of Master of Science in Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania, USA

16 December 2016
ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Necitumumab is an effective add on treatment to traditional chemotherapy regimes when treating stage IV lung or colon cancer.

Study Designs: Review of two open label, randomized, controlled phase III trials and one single arm multicenter phase II study.

Outcomes Measured: Objective tumor response rate was measured for patients with colon cancer. Overall survival rate and length of survival were measured for patients with lung cancer. This was measured in Kapler Meier Methodology.

Results: For two trials the addition of Necitumumab improved overall survival and tumor response rate. The first lung cancer trial did not show improvement of survival rate with Necitumumab. In this trial those receiving the experimental drug had a median survival of 11.3 months compared to 11.5 in those not receiving the experimental medicine. The second lung cancer trial saw survival times as 11.5 months with Necitumumab compared to 9.9 months without it. In the third trial all patients were given Necitumumab in addition to FOLFOX agents for colon cancer. Tumor response rate was compared between those with a KRAS wildtype gene mutation and those with a KRAS mutant gene mutation. The results showed a higher tumor response rate for those with the wildtype mutation, however both groups saw positive reduction in tumors.

Conclusion: The addition of Necitumumab to traditional chemotherapy regimes is an effective way to fight stage IV cancer, especially in those with a KRAS wildtype mutation or with squamous non-small cell lung cancer. It is less effective for non-squamous non-small cell lung cancer.

Key Words: Lung Cancer, Colon Cancer, Necitumumab, Stage IV, metastasis, chemotherapy
INTRODUCTION

Stage IV cancer is often a grave diagnosis for patients. It conjures thoughts of suffering, radiation, and weight loss. As clinicians we must take great care in how we approach managing care for these patients. Optimizing quality of life, managing expectations, and trying our best to fight the spread of tumors are among our goals. Treatment options range from chemotherapy and radiation to surgical excision. An entire field of medicine has been created to fight cancer and we now have fantastic treatment centers and talented specialists across the country. Despite this when a patient presents for the first time and is diagnosed with late stage disease it is extremely rare to see a full recovery. At this stage of the disease our focus is often on prolonging the patients time with us and assuring they maintain a high quality of life while going through treatment. For this reason there are ever evolving chemotherapy regiments being researched and put into trial.

This paper aims to discuss three separate of such chemotherapy trials. The drug in question is called Necitumumab. It is an epithelial growth factor receptor monoclonal antibody. This drug seeks to bind to protein growth factors expressed in tumors and target them for destruction by our immune system. It is a novel medicine because previous chemotherapeutic agents were created using a combination of mouse and human DNA. Necitumumab is created using only human DNA, thus increasing the chance that our bodies will recognize it as “self” and allow it to bind to tumors more effectively. The new medicine is being manufactured under the brand name Portrazza.

The topic of treating late stage cancer is extremely relevant to the practice of Physician Assistants across our country. Not only is Oncology a massive area of research and clinical practice, PA’s are playing an increasingly important role in this specialty. They possess all of the
clinical tools needed to be an effective part of an Oncology team. In 2013 there were 212,584 new cases of lung cancer in this country and 156,176 deaths from this disease\(^6\). Costs associated with a diagnosis like this are astronomical. Some estimates put the costs as high as 90,000 per patient in order to get treatment\(^1\). It is for these reasons that finding more effective and efficient ways to handle late stage cancer is relevant both to PAs and for the medical community in general.

Research into this disease is extensive. It is thought that the origins of tumors are in defective gene expression and the cell cycle. Malignant tumors are pieces of tissue which essentially have rapid cell turnover resulting in an imbalance between cell creation and cell death. This leads to tumor growth and masses forming within the body. The mechanics of tumor growth have their origins in genetics. There are several contributing factors which add to the development of either lung or colon cancer. The leading cause of lung cancer is tobacco smoke. There are massive scale campaigns across the world to encourage smoking cessation and prevent youth from starting the habit. It is often thought that a contributing factor to colon cancer is the “Western diet”. This is a diet high in carbohydrates and low in insoluble fiber\(^4\). Nutrition campaigns seek to educate the public on the importance of eating a balanced diet not only for the reason of nutritional sufficiency, but also as a preventive measure for serious diseases such as colon cancer.

Treatment regiments for cancer include chemotherapy, radiation, surgical excision, or a combination of all three. It is the judgement call of the clinical team and the patient as to which combination of treatment will be most beneficial. Chemotherapy for lung cancer almost always includes a platinum agent such as Cisplatin and one other additional medication. For squamous cell lung cancer Gemcitibine is usually added while for non-squamous cell Pemetrexed is the
additional agent of choice. Colon cancer has been shown to respond best to FOLFOX agents. Portrazza is being proposed as a new agent of add-on treatment because it is made using only human DNA and is thought to be more effective in activating our immune system to attack tumor cells.

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not Portrazza is an effective add-on treatment to traditional chemotherapy regimens when treating stage IV lung or colon cancer.

The populations studied in these trials were composed of individuals over the age of 18 who had histologically confirmed squamous non-small cell, non-squamous non-small cell, or colorectal carcinoma. All individuals in the trials had to have either late stage (III or IV) or metastatic disease. The intervention used on these patients was adding Portrazza to their chemotherapy regime. For the trials involving pulmonary structures average time of survival after initiation of treatment was the measured outcome. This was measured using Kaplin Meier methodology. Comparisons in these studies were between two groups of people; one group received traditional chemotherapy combinations while the other group received the same combination with the addition of Portrazza. These were both open label, randomized, controlled phase III trials. For the study involving structures of the lower GI tract the outcome measured was objective tumor response rate. This was measured using the Response Evaluation Criteria in Solid Tumors, Version 1.0. All members of this trial received Portrazza in addition to FOLFOX agents. The comparison was between one group which had a KRAS wildtype gene mutation and another group which had a KRAS mutant gene mutation. This was a single arm, multicenter, phase II study.
Key words used in searches were “lung cancer”, “colon cancer”, “Portrazza”,
“chemotherapy”, and “stage IV”. All articles were published in American English. They were
searched on PubMed and Cochrane Library Collection and selected based on their clinical
relevance to PAs and whether they included patient oriented outcomes. All articles were
published and the research was done by the author of this paper. Inclusion/ exclusion criteria is
included on Table 1. Statistics used include ARR, RRR, NNT, p-value, and confidence intervals.
Demographic information from the trials is included in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># of pts</th>
<th>w/ d</th>
<th>Age</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elez, E, Hendlisz, A, Delaunoit, T.</td>
<td>Single arm multicenter phase II study</td>
<td>25</td>
<td>0</td>
<td>&gt;18</td>
<td>Advanced unresectable or metastatic adenocarcinoma of the colon or rectum, life expectancy &gt; 6 months, an Eastern Cooperative Oncology Group performance status &lt; 2, adequate organ function.</td>
<td>Prior systemic chemotherapy for locally advanced unresectable CRC, prior radiotherapy to &gt;25% of bone marrow, documented or symptomatic brain metastasis</td>
<td>Addition of Necitumumab to FOLFOX6 agents.</td>
</tr>
</tbody>
</table>
RESULTS

In the trial composed by Paz-Ares, et al, there was not sufficient evidence to support the use of Portrazza as a more effective treatment for late stage lung cancer. In this trial 315 patients received the experimental combination of medicine (Portrazza, Cisplatin, and Pemetrexed) while 318 received the traditional chemotherapy regiment (Cisplatin and Pemetrexed). Unfortunately, the results were not promising, as the authors remark, “there was no significant difference in overall survival between treatment groups”\(^8\). The median survival of the experimental group was 11.3 months while median survival of the group receiving traditional therapy was 11.5 months. P-value in this study was 0.96\(^8\). Data was still collected between the two groups and results are recorded in Table 2. The average survival time was not the only factor which was measured. Mortality rate at one year was also measured and this showed that the experimental group actually had a lower rate than the control. Based on the mortality rate at one year the relative risk reduction of the experiment group was 11% while the absolute risk reduction was 2.5%. There were 79 participants in the experimental group still living after one year compared to 72 of the control group. The numbers needed to treat in this experiment was 40, meaning 40 patients

| Paz-Ares L, Mezger J, Ciuleanu TE. (2015)\(^8\) | Open label randomized controlled phase 3 trial. | 633 | 54 | >18 | No previous chemotherapy, adequate organ function, measurable disease as defined by RECIST 1.0 criteria, histologically confirmed stage IV cancer. | Brain metastasis, third-space fluid retention, peripheral neuropathy grade 2 or worse, major surgery therapy within 4 weeks prior. | Addition of Necitumumab to Pemetrexed and Cisplatin. |
would need to receive the experimental medicine in order to attain one more beneficial outcome. The CER and EER were measured based on the number of patients who were still living after one year.

Further trials for this medicine were warranted and are discussed later in this paper.

Despite the difference in average survival times in first trial it is important to note that the authors do feel that their data is still useful. An important factor in this trial is that the histology of disease being treated was non-squamous non-small cell lung cancer while in the following trial patients with squamous non-small cell were being treated. It is possible that one type of cell is more responsive to the experimental treatment than other types.

### Table 2

<table>
<thead>
<tr>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Relative Risk Reduction</th>
<th>Absolute Risk Reduction</th>
<th>Numbers Needed to Treat</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.6%</td>
<td>25.1%</td>
<td>11%</td>
<td>2.5%</td>
<td>40</td>
<td>Control 43-54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exp. 42-53%</td>
</tr>
</tbody>
</table>

In the trial conducted by Thatcher, et al, the authors again had two sample groups. The first group had 545 patients who received Portrazza in addition to Gemcitabine and Cisplatin. The second group had 548 patients and received only Gemcitabine and Cisplatin. The results were more promising in this study. Authors concluded that “the addition of Necitumumab to Gemcitabine and Cisplatin chemotherapy improves overall survival in patients…and represents a new first line treatment option for this disease”⁹. The average survival time in the control group
was 9.9 months compared to 11.5 months in the experimental group. As with the first trial the data calculated in this paper was based not on the average survival time, but on the number of deaths measured at one year into the experiment. Again the experimental group came out on top with better survival rates. The relative risk reduction for this trial was 21%. Absolute risk reduction was 4%. The number needed to treat was 25, meaning that 25 patients would need to be treated in order for one additional beneficial outcome to be obtained. P-value when measuring average time of survival was 0.01°. It is safe to say that the numbers display a benefit in using the experimental medicine. There were 127 patients living at one year in the experimental group compared to 106 in the control group. Table 3 summarizes this data. The event measured for EER and CER in the table was number of patients alive after one year.

**Table 3**

<table>
<thead>
<tr>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Relative Risk Reduction (RRR)</th>
<th>Absolute Risk Reduction (ARR)</th>
<th>Numbers Needed to Treat</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>19%</td>
<td>23%</td>
<td>21%</td>
<td>4%</td>
<td>25</td>
<td>Control 13-20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exp. 16-24%</td>
</tr>
</tbody>
</table>

The third trial for this medication, performed by Elez, et al, was designed differently than the first two. It was a single arm phase II study and rather than investigating lung cancer the experimental and control groups had stage IV colorectal cancer. All patients in this trial received Portrazza in addition to FOLFOX6 chemotherapy. One variable which the designers of this trial were aiming to measure is whether or not certain genetic mutations in humans are more
responsive to Portrazza than others. This is useful because as we advance research into cancer treatment we may be able to tailor medication to the specific patient and their genetic makeup. The results of this trial demonstrated that those who had the KRAS wild type gene mutation had better outcomes than those who had a KRAS mutant gene mutation. For the purpose of data collection in this trial the experimental group consists of patients with the wild type gene mutation and those in the control group had the mutant type mutation. Total experimental participants were 16 patients and the total control group was 9 patients.

The results show that those with the wild type mutation had a better partial response rate. 10 members of the trial receiving with the wild type mutation had a partial response rate compared to 5 members who had the mutant type mutation. This rate is what was measured to obtain the values in table 4. The control event rate was 55% and experimental event rate was 62.5%. The relative benefit increase was 12.6% and the absolute benefit increase was 7.0%. The numbers needed to treat was 14, meaning 14 patients needed to be treated to obtain one additional favorable outcome. P-value was not reported in this study but the confidence interval for the experimental group was 79-100% and for the control group was 66-100%.

### Table 4

<table>
<thead>
<tr>
<th>Control Event Rate</th>
<th>Experimental Event Rate</th>
<th>Relative Benefit Increase</th>
<th>Absolute Benefit Increase</th>
<th>Numbers Needed to Treat</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>55%</td>
<td>62.5%</td>
<td>12.6%</td>
<td>7.0%</td>
<td>14</td>
<td>Control 66-100% Exp. 79-100%</td>
</tr>
</tbody>
</table>
There are a number of adverse side effects of Portrazza which the authors of these studies measured. In particular, the first two trials, which examined non-small cell lung cancer, measured the rates of a grade 3 rash in their participants. These rates were used to then calculate the numbers needed to harm for both of the clinical trials. In the trial by Paz Ares, et al, 44 members of the experimental group developed a rash compared to only one member of the control group. The control event rate was .00314, experimental event rate was .140, and absolute risk increase .136. Numbers needed to harm for this study was 7, meaning for every 7 patients treated with Portrazza, one more will be affected by an adverse reaction. For the trial performed by Thatcher, et al, 38 members of the experimental group developed a grade 3 rash compared with only two members of the control. The control event rate was .00365, experimental event rate was .07, and absolute benefit increase .067. The numbers needed to harm was 15, meaning 15 patients would need to be treated for one additional patient to have an adverse reaction of a grade 3 rash. This data is summarized in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Control Event Rate (CER)</th>
<th>Experimental Event Rate (EER)</th>
<th>Absolute Risk Increase (ARI)</th>
<th>Numbers Needed to Harm (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paz-Ares</td>
<td>.00314</td>
<td>.140</td>
<td>.136</td>
<td>7</td>
</tr>
<tr>
<td>Thatcher, N</td>
<td>.00365</td>
<td>.07</td>
<td>.067</td>
<td>15</td>
</tr>
</tbody>
</table>

Discussion
This systematic review investigated two randomized control trials and one single arm phase II study. The results were for the most part encouraging. Overall the addition of Portrazza to a traditional chemotherapy increased percentage of living patients after one year and two years of treatment. It also demonstrated that patients with different genetic mutations may be more responsive to treatment with this medication. There were no obvious outliers in these studies.

Sample size and drop-out rates are two factors which limited these clinical trials. Given the high rate of cancer diagnoses in the US it would be useful to have more trials with bigger pools of participants in the future. Additionally, a number of group members in each trial dropped out due to adverse drug reactions from the experimental medicine. This lowered the sample size. The trial measuring treatment of colon cancer was limited in both size and geographic location. The sample groups were very small and were taken in Europe where lifestyle and diet can both have different effects on the body when compared to American culture. Despite any short comings of these trials Portrazza was approved by the FDA in 2015 for use in squamous non-small cell lung cancer.

Portrazza is currently manufactured for an 800mg dose given intravenously over 60 minutes. For a three week cycle of therapy it is to be given on days 1 and 8. Though the most common side effect is a rash there is a warning with this product that cardiopulmonary arrest and hypomagnesemia are both potential adverse effects. This is due to some patients experiencing these in the clinical trials. One of the trials in this paper discussed using Portrazza in colorectal cancer however it is currently only marketed for use in squamous non-small cell lung cancer. Pregnant women are advised against taking Portrazza. There are no studies in regards to breast feeding while on this medication, but women are advised against doing this until at least three months after their last dose. There are no studies regarding using Portrazza in the pediatric
population. There is currently no evidence that poor hepatic or renal function would be contraindications to taking this medication. There is a risk of venous thromboembolism with Portrazza. Manufacturers recommend discontinuing the medication immediately if patients develop an embolism\(^5\).

**Conclusion**

The data collected in these three trials indicates that yes, Portrazza is effective in treating Stage IV metastatic cancer. There is however a catch. It is only effective in squamous non-small cell lung cancer. Two of the trials were performed on other types of cancer, and the medication did not prove effective in prolonging life in non-squamous non-small cell. There is conclusive evidence that those with a KRAS wildtype gene mutation may have a better outcome using Portrazza than those who do not. Future studies may be more effective if they include patients who have earlier stages of the disease. This could help tell us the efficacy of fully curing patients. In the last few decades we have seen massive strides in research behind the pathophysiology of cancer, treatments of this disease, and more effective ways of managing patient care. Portrazza is another step in the right direction in our fight against this tragic disease.

**References**


