

2018

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Recommended Citation

Delibashi, Jera, "Is Epidermal Growth Factor Vaccine also known as CimaVax-EGF more effective at improving survival than best supportive care or other therapies in patients with non-small cell lung cancer?" (2018). *PCOM Physician Assistant Studies Student Scholarship*. 351.

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**Is Epidermal Growth Factor Vaccine also known as CimaVax-EGF
more effective at improving survival than best supportive care or
other therapies in patients with non-small cell lung cancer?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

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

December 15, 2017

ABSTRACT

Objective: The objective of this systematic review is to determine whether or not Epidermal Growth Factor Vaccine also known as CimaVax-EGF is more effective at improving survival than best supportive care or other therapies in patients with non-small cell lung cancer.

Study Design: Systematic review of two randomized control trials (RCTs) and one observational/before and after study published after the year 2007.

Data Sources: All articles were published in English in peer reviewed journals and were searched for personally by me, the author, via PubMed and Embase. Articles selected were only those that were published after 2007, were relevant to my clinical question and addressed patient oriented outcomes that mattered.

Outcomes Measured: Primary outcome measured was overall survival as estimated in months or measured in years. Secondary outcome measured was safety as estimated by percent of patients experiencing any adverse effects and/or specific adverse reactions.

Results: Both Rodriguez et al and Vinageras et al claim that Epidermal Growth Factor vaccine improves overall survival in patients with stage IIIB/IV NSCLC based on the results of their RCTs (Rodriguez et al 343 patients total assessed for efficacy, $p = 0.036$, 5 year survival in vaccinated 16.62% vs control 6.2% NNT = 10, Vinageras et al 74 patients total assessed for efficacy, $p = 0.0124$, 1 year survival in vaccinated 67% vs. control 33% NNT = 3). Kananathan made no claims about efficacy but claimed survival rates indicated the need for a randomized control trial to determine efficacy (23 patients assessed for efficacy, 1 year survival = 91% 5 year survival = 9%). All three studies found the vaccine to be safe and well tolerated.

Conclusions: Although both RCTs claim the EGF vaccine improves survival in Stage IIIB/IV NSCLC patients, risk of bias in study design (not blinded, use of other therapies) and quality of data reported (not reporting some censored patients, overlap of CIs) limit efficacy claims as does the number of studies reviewed. Large double blinded studies are needed to study efficacy.

Key Words: Epidermal Growth Factor (EGF) vaccine and non-small cell lung cancer, CimaVax-EGF and non-small cell lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer death in the world, with non-small cell lung cancer (NSCLC) accounting for 85% of lung cancers in the United States.^{1,2}

In 2017, the estimated number of new cases of NSCLC are 222, 500 and the estimated number of deaths from NSCLC are 155, 870.³ An estimated 13.6 billion dollars were spent nationally for lung cancer in 2016.⁴ In 2006, nearly half a million hospital stays included lung cancer as a diagnosis with almost 28% citing lung cancer as the primary reason for the stay.⁵

The cause of NSCLC (and lung cancer in general) is thought to be largely due to environmental exposure to carcinogens with individual susceptibility to carcinogens and presence or absence of protective factors playing a minor role. Cigarette smoking in particular accounts for about 85% of lung cancers in the U.S.²

Surgical resection of NSCLC tumors is typically considered first line treatment, particularly in early stages. Radiation therapy and/or chemotherapy pre or post operatively or as part of first line treatment for late stages are also commonly used. Prophylactic cranial irradiation is used to reduce incidence of brain metastases. Identification of mutations, particularly in the EGFR, MAPK, PI3K signaling pathways, has led to targeted therapy that addresses abnormalities in these pathways and associated drug resistance.³

Some of the mentioned treatments may in some cases provide a cure, particularly in early stages, and may in some cases prolong survival, however 1 year survival for patients with NSCLC with wild type tumors was 35% and 5 year survival was 5%.⁶ Epidermal growth factor has been shown to promote cancer cell growth and proliferation and patients with NSCLC with overexpression of this factor have been shown to have a poorer prognosis. A vaccine known as

the Epidermal Growth Factor vaccine has therefore been developed with the goal of prolonging survival by inducing autoimmunity against this self-protein.⁶

This paper evaluates two randomized control trials (RCTs) and one observational/before and after study investigating the efficacy of Epidermal Growth Factor Vaccine as a treatment for NSCLC as measured by overall survival.

OBJECTIVE

The objective of this systematic review is to determine whether or not Epidermal Growth Factor Vaccine also known as CimaVax-EGF is more effective at improving survival than best supportive care or other therapies in patients with non-small cell lung cancer.

METHODS

Criteria used for selection of studies were as follows: addressed the population of patients with NSCLC, used Epidermal Growth Factor (EGF) vaccine also known as CimaVax-EGF as an intervention, used supportive care and/or other therapies as comparisons, measured overall survival, and were either randomized control trials or observational/before and after studies.

Key words used for searching articles were Epidermal Growth Factor (EGF) vaccine and non-small cell lung cancer, CimaVax-EGF and non-small cell lung cancer. All articles searched were published in English and all articles were published in peer-reviewed journals. The search databases used were PubMed and Embase. Articles were selected based on their relevance to my clinical question and if they included patient oriented outcomes (POEMs).

The inclusion criteria for selection were RCTs or observational/before and after studies published after 2007. The exclusion criteria for selections were studies published 2007 or earlier, studies that did not measure POEMs.

Statistics reported in the articles were median survival estimates, 95% CIs, p-values, hazard ratios. Statistics calculated by author were RBI, ABI, NNT, RRI, ARI, NNH.^{6,7,8}

See Table 1 for demographics and characteristics of included studies.

Table 1: Demographics and Characteristics of Included Studies

Study and Type	# of pts, Age in years	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Rodriguez 2016 ⁷ RCT	<ul style="list-style-type: none"> • 405 pts • Ages not listed but articles mentions pts matched for age 	<ul style="list-style-type: none"> • Patients 18 or older with histologically or cytologically proven stage IIIB/IV NSCLC and an ECOG performance status of 0-2 • Patients with all NSCLC subtypes and life expectancy of at least 3 months • Hemoglobin values > 90 g/L • Leukocytes count $\geq 3.0 \times 10^9$/L • Platelet count $\geq 150 \times 10^9$/L • Aspartate aminotransferase and alanine aminotransferase up to 2.5X the upper institutional limit • Creatinine up to 2X the upper institutional reference value • Received 4-6 cycles of platinum based chemotherapy (mostly cisplatin/carboplatin in combination with vinblastine, etoposide or paclitaxel) • Had stable disease or objective disease 	Not listed in study	54	2.4 mg of Epidermal Growth Factor (EGF) vaccine given IM at four injection sites (two deltoid and two gluteal) every 2 weeks for 4 doses and then monthly thereafter as well as best supportive care with 200 mg/m ² cyclophosphamide given IV 72 hrs prior to first immunization
Vinageras 2008 ⁸ RCT	<ul style="list-style-type: none"> • 80 pts • Median age 55.5 	<ul style="list-style-type: none"> • Pts older than 18 with histologically or cytologically proven non small cell lung cancer at stages IIIB/IV • ECOG performance status of at least 2 • Adequate bone marrow reserve • WBC count of at least 3,000 per microliter • Platelet count of at least 100,000 per microliter • Hemoglobin of at least 10 g/dL • Life expectancy of longer than 3 months • Normal creatinine, bilirubin, and transaminase according to each institutional standards 	<ul style="list-style-type: none"> •Pregnancy or lactation •Secondary malignancies •History of hypersensitivity to foreign proteins 	6	<ul style="list-style-type: none"> • EGF vaccine on days 1, 7, 14, 28 and monthly after with 200 mg/m² cyclophosphamide given 3 days before 1st dose • External beam radiotherapy for palliative care • Supportive care if required
Kananathan 2015 ⁹ Observational/ Before and After	<ul style="list-style-type: none"> • 23 pts • Median age 55.18 	Patients with stage III/IV non small cell lung cancer	Not listed	1	Four IM injections of Cimavax(EGF vaccine) given day 0, 14, 28, and every 28 days thereafter with 300 mg IV cyclophosphamide given 72 hrs prior to first vaccination

OUTCOMES

The primary outcome measured in all three studies was overall survival, estimated in months by the Kaplan Meier method in the Rodrigues et al and Vinageras et al studies, 1 year survival for the Vinageras et al and Kananathan et al study studies, 2,3,4 year survival for the Kananathan et al study and 5 year survival by the Rodrigues et al and Kananathan et al studies. Safety was a secondary outcome measured as estimated by percentage of patients experiencing any and/or specific adverse events.^{6,7,8}

RESULTS

Description of Studies

Rodriguez et al conducted a randomized control trial that started with 405 patients with stage IIIB and IV NSCLC, 270 of which were enrolled in the vaccination arm, 135 of which were enrolled in the control arm. Patients in the control arm were treated with best supportive care. The two arms were matched for gender, ethnic origin, smoking history, ECOG score, disease stage, tumor histology, and response to first line treatment. Of the 270 patients enrolled in the vaccination arm, 219 received four doses of the vaccine as per protocol (regimen necessary for vaccine induction) and were assessed for efficacy. In the control arm, 124 were assessed for efficacy. Reasons for dropout included death prior to completion of induction period, rapid worsening of performance status, other comorbidities as well as schedule violations and consent withdrawal.⁶

Vinageras et al conducted a randomized control trial that initially involved 80 patients with stage IIB and IV NSCLC, 40 of which were enrolled in the vaccination arm and the other 40 of which enrolled in the control arm. Patients in the control arm were treated with best supportive care. External beam radiotherapy was performed for symptomatic relief in both the

vaccine and control arm. The two arms were matched for age, gender, race, ECOG score, disease stage, tumor histology, prior treatment and response to chemotherapy. Six patients were removed from assessment, three from the vaccine arm and three from the control arm. Reason for nonassessability was given as noncompliance with entry criteria and refusing participation after random assignment.⁷

Kananathan et al conducted an observational/before and after study involving 23 patients with stage III or IV NSCLC all of which were vaccinated with CIMAvax (EGF vaccine). Age, ethnicity, gender varied among the group with a disproportionate number of male patients (16 males to 7 females) and disproportionate number of Malaysian individuals (18 Malaysian compared to 2 Indonesian, 2 Australian, and 1 Chinese patient). Additionally, patients were on different first line therapies simultaneously while receiving vaccination, with chemotherapy being the most common first line therapy (15 patients).⁸

Risk of Bias in Included Studies

Both the Rodriguez et al and Vinageras et al studies were controlled trials in which the control and treatment groups were similar in terms of demographics, and assignment of patients to treatments was randomized, however, the randomization allocation was not concealed from those enrolling in the study, clinicians and study workers were not kept blind to treatment which introduces the possibility of bias. The losses to follow up were less than 20%, and follow up of patients was sufficient long.^{6,7} Kananathan et al was an observational/before and after study. Men compared to women and individuals of Malaysian descent were disproportionately represented which are significant concerns for bias.⁸

Cyclophosphamide was given prior to first vaccine dose in the vaccine arm in both the Rodriguez et al and Vinageras et al studies but not given in the control group.^{6,7} In the

Rodriguez et al study, sixteen patients in the vaccine arm and nine patients in the control arm received other therapies with one patient in each arm receiving a drug known to increase survival in advanced stage NSCLC.⁶ A large number of patients in the Kananathan et al study received a variety of different first line treatments in addition to vaccination.⁸ These confound any efficacy claims by the study authors.

Safety

Of the 270 patients enrolled in the vaccine arm in Rodrigues et al, 246 received at least one vaccine dose and were thus considered the safety population and used for safety analysis while 132 out of 135 patients in the control group were used for safety analysis (three patients in the control group withdrew consent). In the vaccine arm, 195 patients (78.3%) reported any adverse event while in the control arm, 73 patients (55.3%) reported any adverse event.⁶ The relative risk increase (RRI) is 0.416, the absolute risk increase (ARI) is 0.230, and the number need to harm (NNH) is 4 (see Table 2). The most common adverse events reported were injection site reactions, 46.6% in vaccine arm vs 0% in control arm, fever 36.5% in vaccine arm vs 7.6% in the control arm, dyspnea 31.7% in the vaccine arm vs 28.8 % in the control arm, vomiting 23.3% in the vaccine arm and 3.8% in the control arm, and headache 22.5% in the vaccine arm vs 6.8% in the control arm.⁶

Of the 40 patients enrolled in the vaccine arm in the Vinageras et al study, 40 were analyzed for safety and of the 40 patients enrolled in the control arm, 40 were analyzed for safety. The incidence of any adverse event in the vaccine and in the control arm was not reported, however the most common reported symptoms were fever, 25% in the vaccine arm and 7.5% in the control arm, headache, 25% in the vaccine arm and 10% in the control arm, asthenia 20% in the vaccine arm and 18% in the control arm, tremor 18% in the vaccine arm and 0% in

the control arm, and chills 18% in the vaccine arm and 0% in the control arm.⁷ The relative risk increase (RRI) for fever, the most common side effect, is 2.33, the absolute risk increase (ARI) is 0.175, and the number need to harm (NNH) is 5 (see Table 2).

Kananathan et al simply report pain and chills with rigors as being the most common side effects.⁸

Table 2 – Relative Risk Increase, Absolute Risk Increase and Numbers Needed to Harm as Determined by Percent of Patients Experiencing One or More Adverse Events

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to Harm (NNH)
Rodriguez et al	0.553	0.783	0.416	0.230	4
Vinageras et al	0.075	0.25	2.33	0.175	5

Efficacy

In the study conducted by Rodriguez et al, in the per protocol population, median survival was 12.43 months (95% CI 10.42-14.45) in the vaccine arm and 9.43 months (95% CI 7.53-11.33) in the control arm. Five year survival was 16.62% in the vaccine arm and 6.2% in the control arm. The authors conducted a standard, unweighted log-rank test on survival data and found HR 0.77, 95% CI 0.61-0.98, $p = 0.036$ and as such the survival difference was considered statistically significant.⁶ Using 5 year survival for the control arm as the control event rate and 5 year survival for the vaccine arm as the experimental event rate, relative benefit increase (RBI) was 1.682, absolute benefit increase (ABI) was 0.104, and number needed to treat was 10 (refer to Table 3).

Of note, patients with higher than median serum Epidermal Growth Factor (EGF) concentrations that were vaccinated were found to have a statistically significant survival advantage over controls with the same EGF concentrations (HR 0.41 95% CI 0.25-0.67 $P = 0.0001$). Median survival for this subset of vaccinated patients was 14.66 months (95% CI 8.34-20.98) and 8.63 months for this subset of controls (95% CI 1.67-15.59). Five year survival in

this subset of vaccinated patients was 23% while 5 year survival in this subset of controls was 0%. Additionally patients who were determined to have a good antibody response to the vaccine after the completion of the induction period were found to have a statistically significant survival benefit when compared to controls (median survival was 14.90 months in the vaccine arm vs 8.86 months for the control arm (HR 0.638 95% CI 0.44-0.92 p = 0.017)).⁶

In the study conducted by Vinageras et al, in the vaccine arm, median survival was 6.47 months (mean survival 12.73 months) and in the control arm, median survival was 5.33 months (mean survival 8.52 months). These changes were not significant. A significant difference in survival however was found in patients 60 years old or younger. In vaccinated patients 60 years old or younger, median survival was 11.57 months (mean survival 18.53 months) while in the control arm, median survival was 5.33 months (mean survival was 7.55 months, P = 0.0124). One year survival rate was 67% for all vaccinated patients and 33% for controls. One year survival for patients 60 years old or younger was 75% in the vaccine arm and 25% for controls.⁷ Using 1 year survival in all age groups for the control arm as the control event rate and 1 year survival for the vaccine arm in all age groups as the experimental event rate, relative benefit increase (RBI) as 1.03, absolute benefit increase (ABI) was 0.34, and number needed to treat was 3 (refer to Table 3).

Of note, just as in Rodriquez et al, there was a survival advantage found in vaccinated patients determined to have a good antibody response compared to controls (median survival in vaccine arm was 11.7 months (mean 19.47 months) while median survival in control arm was 5.33 months (mean 8.52 months). Additionally there was a survival advantage in vaccinated patients with good antibody response compared to vaccinated patients with poor antibody

response (median survival in vaccinated patients with poor antibody response 3.6 months (mean 4.49 months)).⁷

In the study conducted by Kananathan et al, median survival was 21 months, mean survival was 30.2 months. Survival rate was 91% at 1 year, 43% at 2 years, 30% at 3 years, and 9% at 5 years.⁸

Table 3 – Relative Benefit Increase, Absolute Benefit Increase and Numbers Needed to Treat as Determined by 5 year and 1 year survival

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to Treat (NNT)
Rodriguez et al*	0.062	0.1662	1.680	0.104	10
Vinageras et al**	0.33	0.67	1.03	0.34	3

*Event is 5 year survival rate in decimal form

**Event is 1 year survival rate in decimal form

DISCUSSION

Summary of Main Findings

Rodriguez et al found that there was a statistically significant survival advantage for patients vaccinated with the EGF vaccine ($p = 0.036$) while Vinageras et al found a statistically significant survival advantage in vaccinated patients only in patients 60 years old or younger. Furthermore, Rodriguez et al found a statistically significant advantage in survival for vaccinated patients with higher than median EGF concentrations in serum. Both Rodriguez et al and Vinageras et al found a survival advantage in vaccinated patients with good antibody response as determined by each trial's criteria which was statistically significant in Rodrigues et al however no mention of statistical significance was made by Vinageras et al.^{6,7} Kananathan et al made no claims regarding efficacy as is appropriate since this study is an observational, not experimental study and therefore no claims about efficacy can be made from such a study. The authors simply comment that Phase III clinical trial results are necessary to determine efficacy.⁸

In terms of safety, all three studies determined the vaccine to be well tolerated.^{6,7,8}

Interestingly, for the Rodriguez et al study, the NNH was lower than the NNT but the types of reported side effects would generally be considered reactions that do not threaten mortality or significantly affect overall quality of life as compared to the advantage of overall survival.

Limitations of Evidence

Both Rodriguez et al and Vinageras et al used the Kaplan Meier method to estimate survival time and the standard log-rank test to compare survival between the vaccine and control groups which are appropriate and common for this type of data.

In Rodriguez et al, the small horizontal distances between data points in the Kaplan Meyer curves for survivorship indicate a large number of enrolled subjects suggesting the sample size is more likely to represent the true population. There are also a considerable number of censored subjects in these curves which indicates that the survivorship estimates may not be that accurate. Censored patients were not shown for the survivorship curves in the high EGF serum concentration subpopulation and no reason was given as to why which limits the reliability of this data. There is overlap of the confidence intervals (CIs) for median survival in months for the vaccinated and control groups in the entire population studied as well as in the subpopulation of patients with higher than median EGF serum concentrations, indicating that the true population median in the vaccinated and control groups is possibly the same or median survival is higher in the control group than in the vaccine group. The median survivals are however a snapshot in time and survival differences over time are best compared with the log rank test the results of which showed the data to be statistically significant. The CI for the hazard ratio (HR) (95% CI 0.61-0.98) however indicates that the risk of death for vaccinated patients could be very close to the risk of death for control patients at any point in time (if population HR was 0.98). In the

subgroup of patients with higher than median EGF serum concentrations, CIs for median survival for both the vaccine and control groups were quite wide indicating a wide variability in overall survival within the group and/or a very small number of patients in this group. No CIs for median survival in months was reported for vaccinated patients with good antibody response as compared to the control group. It is important to keep in mind though that the vaccine and control group were not equal in terms of number of patients studied for efficacy, with about 2/3rds of the total number of patients studies for efficacy belonging to the vaccine arm and only 1/3rd belonging in the control arm.

In the Vinageras et al study, censored patients are indicated in all the survivorship curves, and the number of censored patients appear to be few, however, this is a much smaller study than the Rodriguez et al study so to some extent that is expected. No CIs are reported for median survival in months, however both medians and means are reported. There was a large difference between the mean and medians of both the vaccinated and control groups when measuring survival in months for all patients indicating there are one or more outliers in the group that skew some of the data in the direction of increased survival.

CONCLUSION

Although both RCTs claimed EGF vaccine to be effective in improving overall survival in patients with NSCLC, there is insufficient evidence to claim EGF vaccine is effective in improving survival because besides the obvious fact that this review only studies a very small number of studies, there are problems with the study designs (risk of bias) and quality of the evidence (nonreporting of censored patients, median survival CIs). Suggestions for future studies would be designing double blind randomized control trials. In the United States, the first Phase I/II randomized control trial is currently underway in the Roswell Park Cancer Institute.⁹

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