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Sex Differences in Outcome with Bevacizumab Therapy: Analysis of Patients with Advanced-Stage Non-Small-Cell Lung Cancer Treated with or without Bevacizumab in Combination with Paclitaxel and Carboplatin in the Eastern Cooperative Oncology Group Trial 4599

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Abstract

Introduction—E4599 compared carboplatin and paclitaxel with (PCB) or without (PC) bevacizumab in patients with advanced stage non-small cell lung cancer. Bevacizumab improved overall survival. However, an unplanned subset analysis did not show a survival benefit for females treated with bevacizumab.

Methods—Known prognostic factors and toxicities were compared by sex. Proportional hazards models of survival with multiple factor combinations were used to adjust for treatment effect.

Results—The analysis includes 850 patients. The median survival for males was 8.7 months (PC) versus 11.7 months (PCB) (P=0.001) and 13.1 months (PC) versus 13.3 months (PCB) for females (P=0.87). Progression free survival and response rate was 6.3 months and 29% on the PCB arm for males, and 6.2 months and 41% for females, (p>0.05). Progression free survival and response rate was 4.3 months and 16% on the PC arm for males, and 5.3 months and 14% for females, (p>0.05). No significant demographic differences were seen between the two arms for males (M), whereas fewer females (F) on the PCB arm had liver metastasis (PCB 11.7% vs. PC 23.2%, p=0.003). Adverse events with a sex difference on the PCB arm included severe hypertension (M 4.2%, F 9.9%, p=0.02), constipation (M 1.4%, F 4.7%, p=0.05), and abdominal pain (M 0.9%, F 5.2%, p=0.01). In the proportional hazards model adjusting for the other factors, the test for a sex by treatment interaction was not significant (p=0.09).

Conclusions—Multiple factors may contribute to the apparent sex-specific differences in efficacy of bevacizumab noted in this study.

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Keywords

non-small cell; lung cancer; sex differences; bevacizumab

Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States in both men and women[1], killing more women than breast, ovarian, and colon cancer combined. Poor outcome is attributable to the fact that at least 40% of patients present with advanced disease, which is incurable with current treatment regimens. Prior to 2006, doublet chemotherapy (platinum or non-platinum based) served as the standard of care,[2, 3] affording a median survival of 8 to 10 months. With the recognition of the importance of angiogenesis in cancer growth and metastasis, various therapies have been developed to block this pathway, including tyrosine kinase inhibitors of vascular endothelial growth factor receptors (VEGFR) and antibodies against vascular endothelial growth factor (VEGF).[4–6]

Bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), was approved by the FDA for use in combination with paclitaxel and carboplatin for patients with advanced stage, non-squamous NSCLC.[6, 7] The approval followed the positive results from the large randomized Eastern Cooperative Oncology Group (ECOG) trial 4599.[8] ECOG 4599 compared chemotherapy alone (paclitaxel and carboplatin -PC) with the same regimen plus bevacizumab (PCB) in patients with non-squamous advanced stage NSCLC. The PCB combination resulted in a two month improvement in median overall survival (10.3 months PC versus 12.3 months PCB).[8] However, patients on the PCB arm had higher rates of toxicities including neutropenia, hemorrhage, hypertension, and proteinuria. A higher incidence of treatment-related deaths was also observed. Most of these toxicities are known side effects of bevacizumab.

Several studies have demonstrated that females survive longer than males with NSCLC, regardless of stage.[9–13] Females also experience increased toxicity when treated with chemotherapy compared to males.[14] Wakelee and colleagues studied ECOG 1594, which randomized patients with advanced stage NSCLC to 4 different platinum based chemotherapy regimens.[14] Females had a longer median survival (9.2 months for females and 7.3 months for males (p=0.004)). Survival was also better for females at 1, 2 and 3 years (females 38%, 14% and 7% respectively, versus 31%, 11% and 5%, respectively, for males). The survival difference remained statistically significant after adjusting for performance status, weight loss > 10%, presence of brain metastases and stage (IIIB versus IV). This difference in survival remained in both sex cohorts across all of the chemotherapy regimens studied. In terms of toxicity, females tended to have more nausea, vomiting, alopecia, neurosensory deficits and neuropsychiatric deficits. Reasons for this remain unclear.

In an unplanned, exploratory, retrospective, subset analysis of ECOG 4599, sex differences in outcome were also seen.[8] While both sexes had an improved response rate and PFS on PCB compared to PC, females on the PCB arm did not have a longer survival than females treated with PC alone. However, females lived longer than males on both arms by at least 2 months. Because of these inconsistent results and exceptional median overall survival in females, we conducted a subset analysis of ECOG 4599 to evaluate the potential causes of the apparent lack of differences in survival with bevacizumab in females and the excellent overall survival of the females in this trial.

Materials and Methods

As a randomized phase II/III trial, ECOG 4599 evaluated whether the addition of bevacizumab to standard chemotherapy (paclitaxel and carboplatin) improved overall survival in patients with untreated advanced NSCLC. This trial included patients with previously untreated stage IIIB (with a pleural effusion) and stage IV disease, ECOG performance status (PS) of 0 or 1, and adequate bone marrow, hepatic and renal function. This trial excluded patients with squamous cell histology, with significant hemoptysis, with uncontrolled hypertension, on therapeutic anticoagulation, with brain metastasis, and with a recent history of bleeding or thrombosis. Stratification factors were measurable versus nonmeasurable disease, prior radiation versus no prior radiation, prior weight loss < 5% versus ≥ 5%, and stage IIIB with pleural effusion versus stage IV or recurrent disease. Patients were treated with paclitaxel (200 mg/m^2 IV on day 1) and carboplatin (area under the curve of 6 mg/mL x min IV on day 1) and randomized to treatment with or without bevacizumab (15 mg/kg IV on day 1). Patients were treated every 21 days (one cycle) and tumor assessments were performed every 2 cycles (every 6 weeks). Patients with stable or responding disease after six cycles on the PCB arm then received bevacizumab as a single agent until progression or unacceptable toxicity. Trial design did not allow for patient cross-over to the bevacizumab arm. The study employed the standard response evaluation criteria in solid tumors (RECIST) to determine response and the National Cancer Institute Common Terminology Criteria version 2.0 to grade toxicities. The study was carried out in accordance with the Declaration of Helsinki, current FDA Good Clinical Practices, and local institutional ethical and legal requirements

The goal of the current analysis was to evaluate potential reasons why the addition of bevacizumab to PC among females did not appear to result in an improvement in overall survival compared to PC and why females in general survived much longer than expected. Comparisons of toxicity, prognostic factors and efficacy between males and females were performed.

Statistical Methods

Differences in baseline patient demographics and disease characteristics were compared using Fisher's exact test, as were response rates. Overall survival (OS) was defined as the time from randomization to death from any cause. Progression-free survival (PFS) was defined as the time from randomization to disease progression or death without progression; patients who died without documented progression were censored at the date of their last disease assessment. The Kaplan-Meier method was used to estimate the time-to-event distributions and Cox's proportional hazards models, stratified on disease measurability (yes vs. no), disease stage (IIIB vs. IV/recurrent), prior RT (yes vs. no) and prior weight loss (<5% vs. ≥5%), were used to estimate hazard ratios and test for significance for OS. PFS and duration of response distributions were compared using logrank tests. All p-values are two sided and no adjustments have been made for multiple comparisons.

Results

Patient Demographics

Of the 878 participants enrolled in the study, 850 eligible subjects are included in this analysis. Table 1 describes baseline patient demographics and disease characteristics. Females accounted for 46% (n=387) of the subjects on this trial. Fewer females on PC compared to PCB had liver involvement (11.7% versus 23.2% respectively, p=0.003), and compared to males on either the PC arm or PCB arm (20.6% and 20.0%, respectively). A slightly higher proportion of females on the PCB arm had ≥ 5% weight loss prior to starting

therapy compared to the females treated on the PC arm (32.4% versus 24.4%, p=0.09). Fewer females on the PC arm had greater than two metastatic sites involved compared to females on the PCB arm (45% versus 52.2%). The characteristics of the male subjects were balanced on each arm of therapy.

Efficacy

Response rate was assessed on 773 subjects with measurable disease. (Table 2) In the bevacizumab treatment group, response rates were 34.9% compared to 15.1% in the chemotherapy alone arm (p<0.001). Both males and females experienced a higher response rate when treated with PCB (28.8% versus 15.7% for men, respectively, p=0.001, and, 41.1% versus 14.2% respectively for women, p<0.001. Stable disease rate at ≥ 8 weeks was similar between males on each arm (41.7% PC vs. 41.4% PCB), whereas females had a slightly higher stable disease rate on PC, 47.5%, versus 32.1% on PCB therapy. The duration of response was longer when treated with PCB versus PC for the overall group. For men, the duration of response was 6.8 months with PCB and 5.0 months with PC (p=0.05). For females, the duration of response was 5.9 months with PCB and 4.9 months with PC (p=0.06).

The addition of bevacizumab prolonged PFS for both males and females. Males had a median PFS of 4.3 months with PC versus 6.3 months with PCB for a hazard ratio of 0.64 (95% CI, 0.53–0.78, p<0.0001). Females had a median PFS of 5.3 months with PC treatment versus 6.2 months with PCB with a hazard ratio of 0.71 (95% CI, 0.57–0.88, p=0.002).

While overall survival was prolonged for the entire group when treated with PCB (12.3 months vs. 10.3 months for PC), this effect appeared limited to males[8] who had a median overall survival of 8.7 months when treated with PC alone and 11.7 months when treated with PCB HR=0.70 (95% CI, 0.57–0.87, p=0.001). Outcomes for females were similar on both arms. The median overall survival for females treated with PC alone was 13.1 months and was 13.3 months when treated with PCB (HR=0.98, 95% CI 0.77–1.25, p=0.87).

The analysis explored potential imbalances in maintenance bevacizumab therapy on the PCB arm as well as treatment imbalances between females and males. The percent of males and females receiving more than 6 cycles of maintenance bevacizumab therapy was similar, 18.9% versus 22.4%, respectively. Similarly, the percentage of males and females receiving any maintenance bevacizumab doses was 52.9% versus 52.7%, respectively. In addition, males and females on each arm received the same median number of chemotherapy cycles. On the PC arm, the median chemotherapy cycles delivered were 4 for males and 5 for females. On the PCB arm, the median number of cycles of therapy was 7.5 for males and 7 for females. No differences were observed in the distribution of cycles between males and females on each arm.

Tables 3 and 4 display potential imbalances in therapy given at the time of progression. Unfortunately, for at least 35% of the patients on each treatment arm, subsequent treatment was not reported, limiting our analysis. Of those patients where the study documented second-line treatment, approximately 20–27% of patients were administered some type of chemotherapy in the second-line setting. A lower number of females received second-line therapy on both treatment arms compared to males. On PC alone, 20% of the females received second-line therapy compared to 27% of the males. On the PCB arm, 20% of the females received second-line chemotherapy compared to 24% of the males. No differences were noted between the type of second-line therapy given and treatment arms or sex in table 4. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors were prescribed in similar proportions in males and females across the treatment arms (9–16%). Due to the

numbers of subjects without this information recorded, a statistical analysis could not be performed.

Toxicity

Toxicities were assessed in 867 subjects at the time of this analysis. Grade 3 and higher toxicities were compared between sexes and treatment groups. In ECOG 4599, case report forms only recorded grade 3 and greater toxicities (grade 4 or higher for hematologic events). Toxicities to therapy are noted in Table 5.

Subjects treated on the bevacizumab arm experienced more antiangiogenesis therapy toxicities such as hypertension and hemoptysis. Comparing males and females on each arm, females treated with bevacizumab had a higher rate of grade ≥ 3 hypertension compared to males (9.9% versus 4.2% respectively, p=0.02). Hemoptysis, other bleeding events, and proteinuria occurred similarly between males and females on the bevacizumab arm.

Patients treated with bevacizumab and chemotherapy experienced more hematologic toxicities.[8] . Neutropenia, anemia, and thrombocytopenia occurred at similar rates in males and females treated with bevacizumab, although there was no difference between females on the PC arm and PCB arm. Females tended to have more grade 5 neutropenia or infections with neutropenia than males when treated with bevacizumab and chemotherapy. However, no significant differences between the sexes in infection rates were found on the PCB arm. Other general therapy toxicities such as nausea, constipation, and anorexia were similar between the two treatment arms. Females tended to experience more nausea than men across the treatment arms, although the difference was not statistically significant. Females treated with PCB had a higher rate of constipation, 4.7%, compared to males, 1.4% (p=0.05). Correspondingly, females also had a higher rate of abdominal pain on the PCB arm compared to males (5.2% versus 0.9%, respectively, p=0.01). There was no statistically significant difference in the incidence of fatal adverse events between males and females on the PCB arm (1.9% and 5.2%, p=0.07), or between men and women on the PC arm (0.4% and 0.5 %), respectively.

Multivariable analysis

The proportional hazards model adjusted for treatment, sex, and a treatment by sex interaction term was fitted in order to test whether the magnitude of treatment effects differed for females and males. The results for a treatment by sex interaction were statistically significant (p=0.04). After adjusting another model for baseline stratification factors, treatment, sex, PS, stage, liver involvement, bone involvement and adrenal involvement, the following factors demonstrated significantly worse survival: PC treatment (p=0.014), male (p<0.0001), PS ECOG 1 (p<0.0001), recent diagnosis versus recurrent (p=0.00015), liver involvement (p=0.0015), bone involvement (p=0.0009), and adrenal involvement (p=0.003). When a sex by treatment interaction was added to this model thus adjusting for the above factors, it was no longer significant (p=0.09). The estimated treatment hazard ratio for males was 0.73 (CI 0.58–0.90) and for females was 0.97 (CI 0.76–1.26).

Discussion

E4599 demonstrated an overall survival advantage in patients receiving PCB.[8] In an unplanned, exploratory subset analysis, females did not appear to have a survival benefit that males did with PCB, although females on both arms survived longer than males. In fact, the 13.1 month median survival of females in the PC arm was longer than in any previously reported ECOG trial using a chemotherapy doublet in the first line treatment setting for

NSCLC. Although retrospective analyses are limited and should be viewed with caution, causes for the improved survival of females on the control arm remain unclear. Presumably, differences in eligibility criteria do not account for this difference, given that the 8.7 month median survival for males treated with PC on this study is similar to the 8.3 month median survival observed on E1594. Unmeasured differences in second line therapy may be responsible and may have the most effect on overall survival. However the proportion of males and females on both the control and experimental arms receiving second line therapy were roughly the same, although incomplete data collection limits this analysis. It is possible that the surprisingly good survival for females on the PC arm is due to chance alone or other unmeasured prognostic factors such as epidermal growth factor mutations, smoking status, or co-morbidities, limiting our ability to detect an improvement with the addition of bevacizumab.

The poor prognostic characteristics of the males in the PC arm and the females in the PCB arm do not fully explain the differences in survival. Unfortunately, we do not have epidermal growth factor mutation information on the subjects in this study. Epidermal growth factor mutations are known to be more common in neversmokers and are associated with improved prognosis with any treatment. [15] Females on PCB may have been less likely to receive chemotherapy in the second-line setting. However, complete data is not available on second-line therapy prescribed. Females on PCB also experienced more toxicity and had more liver involvement compared to females treated with PC alone. Adjusting for other factors, the difference in the treatment effect between males and females slightly narrowed, but remained substantial.

To our knowledge this is the first detailed report of a sex difference in outcomes from bevacizumab. Reck and colleagues reported subset differences via forest plots of hazard ratios on the AVAiL data (The phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first line therapy for nonsquamous NSCLC). In both the 7.5 and 15 mg/kg bevacizumab dose groups, the overall survival was not statistically improved for males or females. Though for both groups the overall survival was greater than 13 months. Specific data on sex differences and overall survival was not published. Interestingly, for PFS, females had a statistically improved PFS at 15 mg/kg of bevacizumab where males did not and vice versa at the 7.5 mg/kg bevacizumab dose. Data reported provided only minimal details regarding these differences. Unfortunately, due to this lack of information, the AVAiL trial does not substantiate the findings of the ECOG 4599 sex differences data. [16, 17] Other trials of bevacizumab in advanced colon cancer demonstrated a benefit in both males and females.[18]

One possible reason for the differences observed in this study may be related to sex hormones. Wakelee and colleagues examined ECOG 4599 and found an age-sex interaction in that females younger than 60 years of age had an improved survival when treated with PCB but females older than 60 did not.[19] Thus, menopausal status may play a role in these differences as it has with paclitaxel poliglumex.[20]

Other factors that may cause differences in toxicity and potentially a lack of benefit may include factors that affect clearance of bevacizumab. Lu and colleagues described sex differences in the clearance (CL) and central compartment volume of distribution (Vic).[21] Clearance was 26% faster in males than in females. Slower clearance in females could account for the increased toxicity in females on the PCB arm. The postulated reason why clearance is faster in males may be related to greater muscle mass in males compared to females. In our study, no measurements were available other than BMI to allow the examination of differences in muscle mass between females on the two arms. The previous study found an association between low serum albumin concentration (≤ 29 g/L) and a 20%

increase in clearance compared to an average patient treated.[21] Low serum albumin is a marker of poor nutrition and poor liver function which could be caused by liver involvement with disease. However, liver involvement with metastasis is probably not important for bevacizumab since bevacizumab complexes are cleared by the Fc receptor within the endothelial system and not the hepatocyte or biliary system.[22] Thus, an increased proportion of females with liver involvement on the PCB arm would not explain higher toxicity rates. Also in our study, the number of subjects with low albumin levels was similar between the sexes. However, the lower proportion of females with liver metastases in the PC arm may have contributed to why that group did better than expected.

While, both progression free survival and response rate were improved with the addition of bevacizumab in both males and females, our data provides preliminary information that bevacizumab may have different effects on overall survival in males and females with NSCLC. The reasons for this remain unclear and need to be further studied prospectively in future trials with this antibody. Bevacizumab is an active drug in women in NSCLC, where the addition of bevacizumab did result in significant improvements in RR and PFS. The survival in the control group of females treated with PC was unexpectedly high, suggesting that the lack of a difference in survival may be also in part by related to characteristics of this group or due to unknown differences in second-line therapy given in each group. Because of these potential sex differences in treatment benefits and a better overall survival in female patients with advanced NSCLC, sex is an important stratification factor to include in all randomized trials of advanced disease.

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Table 1

Patient Demographics

	PC (n=433)		PCB (n=417)	
Group	**Male (n=253)**	**Female (n=180)**	**Male (n=210)**	**Female (n=207)**
Age ≥ 65	117 (46.2%)	72 (40.0%)	96 (45.7%)	81 (39.1%)
ECOG PS1*	152 (60.6%)	108 (60.3%)	125 (60.1%)	122 (59.2%)
Prior RT	24 (9.5%)	13 (7.2%)	18 (8.6%)	15 (7.2%)
Prior Wt Loss ≥ 5%	77 (30.4%)	44 (24.4%)	50 (23.8%)	67 (32.4%)
Stage IV non-recurrent	200 (79.4%)	137 (76.1%)	160 (76.2%)	150 (72.5%)
Histology: Adeno or NOS	223 (88.8%)	157 (87.2%)	179 (85.2%)	187 (90.3%)
Large cell	17 (6.8%)	12 (6.7%)	12 (5.7%)	5 (2.4%)
BAC	6 (2.4%)	5 (2.8%)	7 (3.3%)	5 (2.4%)
Other Histology	5 (2.0%)	6 (3.3%)	12 (5.7%)	10 (4.8%)
>2 metastatic sites involved	148 (58.5%)	81 (45.0%)	108 (51.4%)	108 (52.2%)
Liver involved	52 (20.6%)	21 (11.7%)	42 (20.0%)	48 (23.2%)

*6 cases were excluded from PS rates due to unknown PS.

Table 2

Efficacy

	PC		PCB	
	Male (n=230)	**Female (n=162)**	**Male (n=191)**	**Female (n=190)**
RR	15.7%	14.2%	28.8%	41.1%
PFS	4.3 mo.	5.3 mo.	6.3 mo.	6.2 mo.
OS	8.7 mo.	13.1 mo.	11.7 mo.	13.3 mo.

* mo. - months

Table 3

Type of First Treatment Given at Progression

Type	PC (n=433)		PCB (n=417)	
	Male	Female	Male	Female
Non-chemotherapy	51 (12%)	26 (6%)	29 (7%)	31 (7%)
Chemotherapy	116 (27%)	89 (20%)	100 (24%)	85 (20%)
Not specified	0	0	1 (<1%)	0
Nothing reported	86 (20%)	65 (15%)	80 (19%)	91 (22%)

Table 4

Specified Types of Treatment Given at Progression (Categories are not mutually exclusive)

Type	PC		PCB	
	Male (n=167)*	Female (n=115)*	Male (n=129)*	Female (n=116)*
Taxane	33	23	35	29
Gemcitabine	41	21	26	14
Other chemotherapy	39	43	37	39
Pemetrexed	4	9	6	7
EGFR	45	32	23	34

* Note that the numbers do not add up because categories are not mutually exclusive.

Table 5

Toxicity

		Treatment Arm							
		PC (n=440) M=258 F=182				PCB (n=427) M=215 F=212			
		3	4	5	p=*	3	4	5	p=*
Toxicity Types	**Sex**	**%**	**%**	**%**		**%**	**%**	**%**	
Neutrophils	M		17.4				27.0		
	F		15.9				24.1		
Platelets	M						1.4		
	F		0.5				1.9		
Hypertension	M	0.4				4.2			
	F	0.5	0.5			9.4	0.5		0.02
Anorexia	M	3.5	0.4			3.3	0.5		
	F	3.8				6.1	0.5		
Constipation	M	3.5	0.4			1.4			
	F	2.7				4.2	0.5		0.08
Nausea	M	4.3				4.7			
	F	7.7				7.5			
CNS hemorrhage	M						1.4		0.25
	F								
Hemoptysis	M					0.5		0.9	
	F	0.5				0.5	0.5	1.4	
Febrile Neutropenia	M	3.1			0.02	5.6			
	F					2.4		0.5	
Infection w/Grade 3 or 4 Neutropenia	M	1.6	0.8			1.9	0.5		
	F	1.6				0.9	0.5	0.9	
Hyponatremia	M	0.8	0.4			2.8	0.5		
	F	1.1				2.4	1.4		

			Treatment Arm								
			PC (n=440) M=258 F=182				PCB (n=427) M=215 F=212				
			3	4	5	p=*	3	4	5	p=*	
Toxicity Types	**Sex**		%	%	%		%	%	%		
Abdominal Pain	M	1.6					0.9				
	F	0.5	0.5				5.2				0.01

M = Males F = Females

* If not otherwise specified, p value >0.05. P values are for comparing Grade 3 or higher by sex within treatment arms.