Original Research

Sex Differences in Hazard Ratio During Drug Treatment of Non–small-cell Lung Cancer in Major Clinical Trials: A Focused Data Review and Meta-analysis

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ABSTRACT

Purpose: Understanding how sex impacts the efficacy of anticancer agents is a crucial step toward personalized and precision medicine. This review and meta-analysis evaluated sex differences in hazard ratios (HRs) of progression-free survival and overall survival in representative Phase III clinical trials of non–small-cell lung cancer (NSCLC).

Methods: Data were extracted from 24 large-scale clinical trials that included 12,000 male and 7000 female patients. The data were examined for HR differences between subgroups by sex, smoking status, and age, and for potential sex–smoking status, sex–age, and sex–drug interactions, during cancer treatment.

Findings: Summarized information revealed variations in the influences of sex, smoking status, and age on the efficacy of drugs used for the treatment of NSCLC. The male and female subgroups had different HR values. Smoking status, age, and the percentage of female patients in a treatment group had no influence on the sex HR. The sex difference was supported by a set of data collected from all journals.

Implications: The findings from this meta-analysis are important for assessing potential toxicity during drug treatment in both sexes. The outcomes measures of a drug in clinical application should be specified by subpopulation, such as males versus females, as a first step in personalized medicine. (*Clin Ther*. 2017;39:34–54) Published by Elsevier HS Journals, Inc.

Key words: age, cancer, drug, gender, lung, smoke.

INTRODUCTION

Sex differences in gene function and disease prevalence are recognized. Variances in health throughout the lifespan due to sex have been well documented.[1–3] Sex-attributable inconsistencies in the prevalence and severity of cancer are well-known phenomena; however, it is only in recent years that the issue has been given real attention and we have begun to understand the possible causes of such differences.[1]

The influences of sex and age on the efficacy of drugs used for the treatment of patients with cancer remain

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complicated issues. In a review from 2012, Schmetzer and Flörcken[2] stated that "There are clear gender-dependent differences in response rates and the probability of side effects in patients treated with chemotherapy. Sex-biased expression levels of metabolic enzymes and transporters in liver and kidney leading to different pharmacokinetics have been described for most common anti-cancer drugs (page 411)". However, there are a considerable number of controversial reports on sex differences in response to cancer drug treatments.[4–7] The major factor causing such an uncertainty is the heterogeneity of the human population. It is extremely difficult to identify sex-, age-, and genotype-matched pairs from large populations to study the sex differences of drug effects in cancer treatment. However, data from large-scale populations of patients on drug treatments for cancer provide an opportunity to examine sex and age differences in response to drug treatment. This review evaluates sex and age differences in hazard ratios (HRs) of progression-free survival (PFS) and overall survival (OS) during drug treatment of different cancers.[8]

Lung cancer has been the most common cancer worldwide for several decades. More males have lung cancer than do females. According to the World Health Organization's GLOBOCAN 2012, the prevalence of lung cancer was 1242 per 100,000 population worldwide (1099 male, 583 female patients) (http://globocan.iarc.fr/Default.aspx). A considerable amount of data from studies on sex differences in drug treatment and the genetic mechanisms of lung cancer are available, but the data are controversial. Wakelee et al[11] reported that female patients with lung cancer survive longer than do male patients. However, Makihara et al[12] studied sex differences in hematologic toxicity among patients with lung cancer receiving amrubicin monotherapy and concluded that sex could be an important predictive factor associated with grade 4 neutropenia. In 2009, Harichand-Herdt and Ramalingam[13] provided a comprehensive review on the sex-related differences in clinical factors and outcomes in patients with lung cancer observed in early years of population-based studies and clinical trials. They observed an improved survival in the female subgroups in a number of clinical trials.

The HR of the PFS/OS ratio has been used for the measurement of drug efficacy in clinical trials. Many trials have reported HR values in analyses by subgroup, such as sex, smoking status, and age. This review intends to compare HR values between female and male subgroups and the influence of smoking status and age on HR.

MATERIALS AND METHODS

Data Collections

To obtain the most informative data, in most cases in our analyses, we focused on publications from the preceding 10 years on the drug treatment of major cancers and non-small cell lung cancers with sex differences in prevalence ratios,[10,11] using the following criteria: (1) publications in major clinical journals, specifically *The Lancet, The New England Journal of Medicine,* and the *Journal of Clinical Oncology*; 2) Phase III clinical trials; (2) trials in >100 patients; and (3) analyses of the influence of sex on the effectiveness of drugs. Accordingly, we collected data using PubMed, using the search terms *lung cancer and phase trial* and journal name, or *female male phase trial lung cancer*. Studies on NSCLC were selected for analysis.

This review collected data from large-scale trials in high-quality journals to represent the thousands of publications on clinical trials in lung cancer. These trials included open-label, randomized, prospective analyses and double-blind, randomized trials. If either sex represented $<10\%$ of either the control or the treatment group, the study was not used for this analysis.

From each published trial that met the inclusion criteria, the following data were extracted: total number of patients; numbers of female and male patients; and mean (range) PFS HR and OS HR (95% CI) values in the subgroups by sex, age (<65 [60] years vs ≥ 65 [60] years), and smoking status (ever-smokers vs never-smokers).

Our analysis was mainly dependent on reported HRs in female and male subgroups as well as in age subgroups. We examined the results from these publications and asked whether: (1) male and female patients respond differently to treatment; (2) age and/or sex influences the efficacy of a drug used for treatment; (3) drugs have different efficacy in female versus male patients having the same cancer type; and (4) the efficacy of a drug shows sex differences in different types of cancer.

Statistical Analysis

A 2-tailed, paired *t* test (blind *t* test) was conducted to determine significance of the difference in HRs