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Relationship between anti-depressant use and lung cancer survival

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ABSTRACT

Objectives: In recent years, the anti-cancer properties of several commonly used drugs have been explored, with drugs such as aspirin and beta-blockers associated with improved cancer outcomes. Previous preclinical work demonstrated that tricyclic anti-depressants have antitumor efficacy in lung cancer. Our goal was to examine the association between anti-depressant use and survival in lung cancer.

Materials and methods: We examined the association between use of common anti-depressants and survival in 1097 lung cancer patients from the NCI-Maryland lung cancer study. The types of anti-depressants included in the study were norepinephrine and dopamine reuptake inhibitors, serotonin reuptake inhibitors, selective serotonin reuptake inhibitors, non-selective serotonin reuptake inhibitors, and tricyclic anti-depressants. Anti-depressant use was extracted from the medical history section of a detailed interviewer-administered questionnaire. Specific use in the three months before a lung cancer diagnosis was determined. Cox portioned hazards modeling was used to estimate the association between anti-depressant use with lung cancer-specific death with adjustment for potential confounding co-factors.

Results: Anti-depressant use was associated with extended lung cancer-specific survival. In an analysis of specific classes of anti-depressant use, NDRIs and TCAs were associated with improved survival. Importantly, the extended survival associated with anti-depressants was maintained after adjustment for the clinical indications for these drugs, suggestive of a direct effect on lung cancer biology.

Conclusions: Considering the manageable and largely tolerable side effects of anti-depressants, and the low cost of these drugs, these results indicate that evaluation of anti-depressants as adjunct therapeutics with chemotherapy may have a translational effect for lung cancer patients.

Microabstract:

- Catecholamine signaling is increasingly recognized in connection with cancer.
- The relationship between antidepressant use and survival was assessed in 1097 lung cancer patients.
- Antidepressants, which modulate catecholamines, are associated with lung cancer survival.
- Of the six drug classes tested, TCAs and NDRIs are the main forms associated with outcome.
- Both TCAs and NDRIs are associated with prolonged patient survival.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide [1]. The 5-year survival rate is approximately 15%. One of the major contributing factors to this dismal survival rate is the stage at which the majority of lung cancers are diagnosed—greater than 50% is diagnosed at stage 3 or 4, a time when both local and systemic treatments are unlikely to be curative. Although early detection of lung cancer among high-risk individuals can reduce lung cancer mortality by up to 20% [2], there is still an immense need for the development of therapeutic approaches to help lung cancer patients worldwide.

Treatment options for lung cancer patients have recently progressed in the age of genomic medicine. For instance, targeted

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treatments for *EGFR* mutations and *EML4-ALK* rearrangements have extended survival times in advanced stage lung adenocarcinoma patients that carry these genomic alterations [3]. To complement ongoing efforts to improve the efficacy of chemotherapy and identify targeted therapies, the anti-cancer properties of several commonly used drugs have been explored in recent years; intriguingly, drugs such as aspirin and beta-blockers have been associated with improved cancer outcomes [4–6]. While these drugs can have toxicities, they are generally better tolerated than those associated with chemotherapeutic drugs and they can be easily combined with standard-of-care treatment.

Anti-depressants are commonly used in both the general population and cancer patients [7]. Previous studies have yielded contradictory results regarding possible links between the use of anti-depressants and cancer [7–15]. In lung cancer specifically, recent work in mice suggests that tricyclic anti-depressants could be an efficacious treatment strategy in small cell lung cancer and neuroendocrine tumors [13]. Based on these observations, we examined the relationship between anti-depressant use and prognosis in a population of patients diagnosed with lung cancer. We found that lung cancer patients taking NDRIs and TCAs have a significantly improved survival. These results may have significant translational impact for repositioning commonly used drugs as anti-cancer therapy.

Methods

Study population

We conducted a nested case-only analysis of patients with pathologically confirmed lung cancer, recruited from the greater metropolitan area of Baltimore, MD as part of the NCI-MD lung cancer case control study between 1998 and 2010. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Boards of all participating institutions. Inclusion criteria for this on-going case-control study have been previously described [16]. Briefly, participants were United States citizens, English-speaking and non-institutionalized. Participants took part in a detailed questionnaire at the time of their diagnosis that collected extensive information on nutrition, reproductive health, medical history, occupational history, smoking, and alcohol consumption. Never smokers were defined as those who smoked < 100 cigarettes during their lifetime. Former smokers were defined as those who reported quitting smoking ≥1 year before the date of interview. Race was self-reported. A summary of the patient characteristics is shown in Table 1.

Extraction of medication use data

As part of the NCI-MD case controls study, patients took part in a questionnaire that gathered demographic, lifestyle and medical history. For this nested case-only study, we identified 1097 lung cancer patients in the NCI-MD case control study with questionnaire data relating to medication use (Table 1). The health questionnaire was developed to include the assessment of medication use during the three months prior to interview. Patients were asked: *Have you taken any prescription or non-prescription medications in the last 3 months?* For those patients that responded yes, the name of the drug was recorded, later extracted and transcribed by hand. Anti-depressant use, including the reasons for its use, was also extracted. Anti-depressant drug classes considered in this analysis were: NDRIs (norepinephrine-dopamine reuptake inhibitors), SNRIs (serotonin and norepinephrine reuptake inhibitors), SSRIs (selective serotonin reuptake inhibitors), SRIs (serotonin reuptake inhibitor), NSSRIs (non-selective serotonin reuptake inhibitors), tricyclics (TCAs), and MAOIs (monoamine oxidase inhibitors). Patients were initially classified as having taken an anti-depressant if they reported using any of these drugs. Subsequently, variables were created to specifically document sole use of each anti-depressant class (Supplementary Table 1). A full list of the drugs within each class from this patient population is outlined in Supplementary Table 2.

Statistical analysis

To test the magnitude of association between anti-depressant use with lung cancer-specific survival, 5-year lung cancer-specific hazard ratios (HR) were estimated using multivariable Cox proportional hazards regression modeling with adjustment for potential confounders, including age (continuous), sex (male/female), current smoking status (never/former/current), pack-years of smoking, race (African American/European American), histology (adenocarcinoma/squamous cell carcinoma/LCLC/other), stage (stage I/stage II/stage III/stage IV), income, education and drug indication. Survival times in the NCI/MD study were gathered through a query of the National Death Index (last entry 12/31/2012) and determined as time from diagnosis to last known follow-up or date of death. Time from lung cancer diagnosis was used to estimate the survival timescale, and failure was described as lung cancer-specific death. Proportional hazards assumptions were verified by visual inspection of log-log plots and using a nonzero slope test of the Schoenfeld residuals. In this study, causes of death other than lung cancer were censored (n=70). As competing risks are distinct from standard censoring, we performed a competing risks regression based on the method of Fine and Gray [17] using the stcrreg function in STATA. A new variable was generated to specify the competing events (death from cancer and death from another cause).

We also addressed whether or not confounding by medication indication could have contributed to our observed findings. This is because the condition that the drug was initially prescribed for could be associated with lung cancer outcome also. Patients were asked why each drug was prescribed; this was then coded as a variable and included in the regression model. All statistical analyses were performed using STATA (*Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Results

Characteristics of the study population

This study included 1097 primary lung cancer cases (Table 1). The median age at diagnosis of the population was 65.8 years. Those taking anti-depressants were diagnosed earlier, more likely to be female, of European American ancestry and current smokers (Table 1). The overall median survival time across all stages was 2.7 years: for those not taking anti-depressants it was 2.6 years and for those who took anti-depressants the median survival was 3.2 years (Table 2). There were 382 patients with stage I lung cancer, 109 with stage II, 244 with stage III and 258 with stage IV; stage information was missing on 104 patients. As shown in Table 1, there were 59, 7, 118, 25, 4, 25, and 1 patients who reported taking NDRIs, SNRIs, SSRIs, SRIs, NSSRIs, TCAs, and MAOIs, respectively (overall, 207 patients reported taking anti-depressants). As there was only one patient that reported taking MAOIs, this patient was removed for single class analyses. Some of the patients in this study reported using more than one type of anti-depressant. The matrix of multiple anti-depressant use is outlined in Supplementary Table 1. The population examined is representative of the general population in the United States, in that the proportion of patients with lung cancer taking anti-depressants was similar to that observed in the general population [18,19]. As previously reported [18,19], women were more likely to use anti-depressants than men (P=0.004).