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Malignant Melanoma in Early-Treated Parkinson's Disease: The NET-PD Trial

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Abstract

Background—The risk for malignant melanoma is higher than expected in Parkinson's disease (PD). The National Institutes of Health (NIH) Exploratory Trials in PD (NET-PD) Long-term Study 1 (LS-1) trial is a contemporary phase 3 study of subjects with early, treated PD. The objective of this work was to assess the incidence of malignant melanoma in a PD cohort.

Methods—Incident melanoma cases were identified from the adverse events log. The expected number of cases was calculated, using the expected incidence rates and the number of person-years.

Results—A total of 618 females and 1119 males were followed for 6452 person-years; 19 new melanoma cases were observed. The expected number was 5.29. The standardized event ratio compared to the general population was 3.6 (95% confidence interval, 2.2-5.6).

Conclusions—The risk for developing melanoma was higher than expected in the NET-PD LS-1 cohort and was similar to the risk reported in earlier comparable clinical trial cohorts. Dermatologic screening may be useful in Parkinson's disease to identify melanoma at an early stage.

Keywords

Parkinson's disease; malignant melanoma; clinical trial; standardized event ratio

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It has been repeatedly shown that the risk for malignant melanoma (melanoma) is increased in Parkinson's disease (PD), although the risk for cancer in general is decreased compared to the general population.[1] A meta-analysis found that the pooled overall odds ratio for melanoma in PD was 2.11 (95% confidence interval [CI], 1.26-3.54).[2]

The first large-scale clinical trial to assess the melanoma risk in PD was the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study in the late 1980s. Secondary data analysis showed that the risk for developing melanoma during a total of 3691 person-years was higher in trial participants compared with the general population (standardized event ratio 3.3; 95% CI, 1.1-7.8). The study was not specifically designed to investigate cancer occurrences in a PD cohort; information about melanoma was retrieved from routinely collected adverse events and medical history data.[3]

A second similar trial was the Parkinson Research Examination of CEP1347 Trial (PRECEPT), enrolling between 2002 and 2004. A total of 806 subjects with early PD were monitored for an average of 1.8 years (1467 person-years total). The incidence of melanoma was 20.9 (95% CI, 9.6-39.7) times higher than expected in the general population. All subjects were required to undergo routine cancer screening examinations within 12 months prior to enrollment and were annually evaluated by a dermatologist during the trial.[4]

The present study aims to investigate the risk for melanoma in PD using data from a third, contemporary, and recently terminated clinical trial: the National Institutes of Health (NIH) Exploratory Trials in PD (NET-PD) Long-term Study 1 (LS-1) (ClinicalTrials.gov Identifier: NCT00449865). Being conducted in consecutive roughly 10-year intervals, in comparable PD cohorts, the results from these 3 separate trials offer a unique opportunity to investigate trends and to evaluate whether the passage of time and the dissemination of knowledge has had any impact on the reported risk for melanoma in PD.

Subjects and Methods

Subjects

The NET-PD LS-1 is a long-term, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study targeting subjects with early, treated PD, to investigate whether additional treatment with creatine impacts the rate of disease progression, measured at 5 years. The study was started in 2007 and was terminated in September 2013. At enrollment, subjects had a diagnosis of PD of no longer than 5 years duration, and were treated with and responsive to dopaminergic therapy for at least 90 days, but not longer than 2 years. Medical history was taken at the screening/baseline visit and adverse events were actively elicited at all visits (months 3, 6, 12, 18, 24, then annually; telephone contacts at 6-month periods beginning with month 30) until 1 month after study completion.

Detailed clinical and demographic data together with inclusion/exclusion criteria and randomization procedures have been published.[5]

Methods

The methods of this analysis are similar to those used in comparable analyses of data from the DATATOP and the PRECEPT cohorts.[3,4] Information about melanoma was extracted through a detailed secondary analysis of medical history, adverse event data, and direct inspection of case report forms. These results are based on a database freeze that occurred on March 15, 2013. All adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) and the following MedDRA-preferred terms were further investigated: any term containing the word “Melanoma,” “Lentigo maligna,” “Skin cancer,” “Metastasis,” “Neoplasm,” “Precancerous skin lesion,” “Skin disorder,” “Skin nodule,” “Micrographic skin surgery,” “Mole excision,” “Plastic surgery,” “Skin lesion excision,” or “Skin neoplasm excision.” When these terms were encountered, the entire medical history and all adverse events were reviewed in order to ascertain a melanoma diagnosis.

Statistical Analysis

The number of person-years observed in NET-PD LS-1 trial was calculated from enrollment to the date of the last observed follow-up visit (for those without melanoma) or to the adverse event date of melanoma (for cases). The expected number of cases was determined by applying the age- and gender-specific incidence rates reported by the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Program (http://seer.cancer.gov/) to the number of person-years observed in each age and gender category. The SEER Program publishes cancer incidence from 20 population-based cancer registries in the United States. Age-adjusted incidence rates from the SEER database were retrieved for maximal harmonization between the NET-PD LS-1 and the SEER cohorts by selecting the following parameters: SEER 18 areas, 2000 to 2010, 2000 U.S. standard population, melanoma of the skin, each gender separately, for each 5-year age category from 20 to 851 years, Non-Hispanic white. The standardized event ratio (SER) with exact 2-sided 95% CI ($SER_L = \frac{\chi^2_{2D,\alpha/2}}{2E}$ and $SER_U = \frac{\chi^2_{2(D+1),1-\alpha/2}}{2E}$) compares the observed number of cases in NET-PD LS-1 to the expected number obtained through SEER.[6,7] Subjects who had melanoma in their medical history were excluded. Fisher's exact tests and *t* tests were used to compare differences between subjects with melanoma and those without.

Results

As of March 15, 2013, a total of 618 females and 1119 males were followed for a total of 6452 person-years. Four subjects who reported melanoma in their previous medical history were excluded. Baseline characteristics for melanoma cases (n 5 19) and non-cases (n 5 1718) are shown in Table 1. Using a significance level of 0.05, there were no statistically significant differences at baseline between melanoma cases and non-cases in regard to demographic and clinical characteristics (Table 1) or type of PD medication used at randomization (eg, levodopa only, dopamine agonists only, or combination therapy). If the NET-PD LS-1 subjects had the same risk of melanoma as the standard U.S. population, the total expected number of cases would have been 5.29. The risk for melanoma was increased in the NET-PD LS-1 cohort, with an overall standardized event ratio of 3.6 (95% CI, 2.2-5.6).

Discussion

The risk for developing melanoma was higher than expected in the NET-PD LS-1 cohort compared with the general population. This finding is in line with previous results showing an increased risk for melanoma in PD. The literature on melanoma in PD is substantial but heterogeneous, and our results from a contemporary clinical trial setting permit direct comparison with previous findings generated over the last 3 decades from similar clinical trial cohorts. We found that, despite the passage of more than 20 years since DATATOP and regardless of the increased awareness regarding risk factors for melanoma in general and the association between melanoma and PD in particular, the reported risk for melanoma in PD seems to be as high now as it was in the past. Increased awareness could have lead to more vigilance and an increased rate of melanoma diagnosis in PD, but this did not occur, according to these results. Contrasted with DATATOP and PRECEPT, the NET-PD LS-1 cohort is much larger in regard to the number of subjects and person-years, which enhances the reliability of these results.

There may be a higher probability of finding melanoma in clinical study participants under close surveil-lance, and particularly in a PD study, because there is a higher awareness regarding the melanoma risk. However, it is not possible to assign the increased risk to this fact alone. Some of the same studies showing increased risk for melanoma in PD found a decreased risk of most other cancers, and there are genetic[8] and biological data[9,10] linking PD and melanoma together.

Ethnicity is a strong predictor of melanoma risk and our calculations were conservative, using the highest expected SEER incidence rate which is for Non-Hispanic whites representing 90% of the NET-PD LS-1 cohort. Due to the very low number of cases expected in a non-white population, race-based comparisons in regard to melanoma risk were not attempted.

A limitation in this and in the DATATOP study, but not in the PRECEPT, was the lack of pathologic confirmation of the melanoma diagnosis, which was based solely on self-report. In addition, there was no validation that the identified melanoma cases were truly incident cases during the study observation time.

The increased risk for melanoma found in this study (3.6; 95% CI, 2.2-5.6) was comparable with what was seen in the DATATOP (3.3; 95% CI, 1.1-7.8) but significantly lower than in the PRECEPT study (20.9; 95% CI, 9.6-39.7). A plausible reason for this discrepancy may be the higher level of vigilance imbedded in the design of the PRECEPT study with mandatory regular dermatologic surveillance, compared with a routine collection of reported adverse events, including melanoma. In that case, it could be argued that a more active attitude in respect to detecting melanoma could facilitate an earlier diagnosis. However, among the 3 studies, the PRECEPT study had the lowest number of person-years and consequently the widest CI.

Our results, confirming previous findings, do not show any trend for a change in the reported risk for melanoma in PD, despite increased awareness over time. Extra vigilance cannot decrease the risk for melanoma but it may affect its outcome through early detection,

as the prognosis is clearly linked to the stage of the disease at the time of treatment initiation.[11] Routine clinician screening for melanoma in conjunction with patient and caregiver education and vigilance are critical for early identification and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Clinical characteristics of nonmelanoma subjects and melanoma subjects at baseline, unless otherwise specified

	Nonmelanoma subjects (n = 1718)	Melanoma subjects (n = 19)	*P*
Males, n (%)	1104 (64%)	15 (79%)	0.232
Age at baseline, y	61.7 (9.6)	65.9 (8.0)	0.062
Age at PD diagnosis, y	60.2 (9.7)	64.1 (8.0)	0.079
Age at MM report, y	NA	67.6 (8.0)	NA
PD duration at baseline, y	1.5 (1.1)	1.8 (1.1)	0.376
PD duration at MM report, y	NA	3.5 (1.9)	NA
Total UPDRS III	17.8 (8.4)	17.2 (6.1)	0.760
Time since start of PD therapy, y	0.8 (0.7)	0.8 (0.6)	0.740
Non-Hispanic, white, n (%)	1548 (90%)	19 (100%)	0.247

Values are mean (SD) unless otherwise specified.

PD, Parkinson's disease; MM, malignant melanoma; NA, not applicable; UPDRS-III, Unified Parkinson's Disease Rating Scale, clinician-scored motor evaluation.