High azathioprine dose and lip cancer risk in liver, heart, and lung transplant recipients: A population-based cohort study

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Background: Iatrogenic immunosuppression is a risk factor for lip cancer but the determinants are unknown.

Objective: We sought to quantify the association between the type, dose, and duration of iatrogenic immunosuppression and lip cancer risk in solid organ transplant recipients.

Methods: We conducted a population-based cohort study of all adult Australian liver, heart, and lung transplant recipients from 1984 to 2006 (n = 4141). We abstracted longitudinal data from medical records and ascertained incident lip cancer (n = 58) and deaths (n = 1434) by linkage with national registries. We estimated multivariable hazard ratios (HR) for lip cancer using the Fine and Gray proportional subdistribution hazards model, accounting for death as a competing risk.

Results: Lip cancer risk (n = 58) increased with high mean daily dose of azathioprine (HR 2.28, 95% confidence interval [CI] 1.18-4.38), longer duration of immunosuppression (HR 9.86, 95% CI 2.10-46.3), increasing year of age at transplantation (HR 1.14, 95% CI 1.04-1.25), earlier transplantation era (HR 8.73, 95% CI 1.11-68.7), and history of smoking (HR 2.71, 95% CI 1.09-6.70).

Limitations: Data on potential confounders such as personal solar ultraviolet radiation exposure were not available.

Conclusion: Higher doses of azathioprine increase lip cancer risk, with implications for managing immunosuppressed populations and our understanding of the relationship between solar ultraviolet radiation and lip cancer. (J Am Acad Dermatol 2016;74:1144-52.)

Key words: azathioprine; cohort; immunosuppression; lip cancer; risk factor; squamous cell carcinoma; transplantation.

Lip cancer is a common cancer in solid organ transplant recipients and occurs at a relative risk of 20 to 80 compared with the general population.[1-4] Another immunosuppressed population, individuals with HIV/AIDS, experiences a 2.8-fold relative risk.[3] This 10-fold difference in risk

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suggests immunosuppressive agents may contribute both directly and indirectly, via immunosuppression, to lip cancer development. A range of evidence supports such effects. In kidney transplant recipients whose graft fails and immunosuppressive therapy is ceased, lip cancer risk declines toward normal.[5] Increasing duration of immunosuppression and the current use of cyclosporine and azathioprine have been shown to increase lip cancer risk in kidney transplant recipients.[6] In addition, lip cancer risk is higher in heart and lung than liver transplant recipients, which parallels the relative dose of immunosuppression by transplanted organ.[7-9] However, the dose-related association with immunosuppressive agents has not been examined.

We examined the relationship between the type, dose, and duration of immunosuppressive therapy and lip cancer risk in Australian organ transplant recipients.

CAPSULE SUMMARY

- Iatrogenic immunosuppression increases the risk of lip cancer.
- We show that higher doses of azathioprine, but not other immunosuppressive agents, are associated with increased lip cancer risk in Australian solid organ transplant recipients.
- Azathioprine should be used with caution in individuals at high risk of squamous cell carcinoma of the lip.

METHODS

Participants

We performed a population-based cohort study of all adult Australian liver, heart, and lung transplant recipients from 1984 to 2006 (n = 4232).[1] Recipients were registered on the Australia and New Zealand Liver Transplant Registry or the Australia and New Zealand Cardiothoracic Organ Transplant Registry. We excluded 89 recipients with no retrievable medical records and 2 with lip cancer before transplantation. We obtained ethical approval from all relevant institutional review boards.

Data collection

We ascertained incident lip cancers (*International Classification of Diseases for Oncology* C000-C009) by linkage between the transplant registers and the Australian Cancer Database, a register of incident primary invasive neoplasms except nonmelanoma skin cancer (NMSC). We identified deaths from the transplant registers or by record linkage with the National Death Index.

The demographic characteristics of recipients and donors and clinical information (transplantation date, organ type, primary indication, subsequent transplantation) were prospectively collected by the registers. We retrospectively collected recipient lifestyle characteristics, weight, comorbidities, immunosuppressive agents, and antiviral prophylaxis from transplantation unit medical records. We ascertained immunosuppressive agents at transplantation and at 3 months, 6 months, and 1, 5, 10, 15, and 20 years after transplantation, including the use and dosage of cyclosporine, tacrolimus, azathioprine, mycophenolate, sirolimus, and everolimus, and the receipt of antibodies at induction and rejection.

Data management

Recipient weight was not recorded at 33% of observation times, and the type and dose of individual immunosuppressive agents was missing at 17% and 37% of all observation times, respectively. We imputed missing recipient weight values from a linear mixed model including age at transplantation, sex, and weight at other observation times for the same individual.[9] We standardized the dose of individual agents to mg/kg/d, and imputed missing data on the type and dose of individual immunosuppressive agents for a maximum of 1 consecutive follow-up time point by carrying the last observation forward, the conventional method for imputing longitudinal medication data.[9,10] The extent of missing data after imputation is shown in Supplementary Table I (available at http://www.jaad.org).

Statistical analysis

Person-years of follow-up accrued from the date of transplantation until the date of lip cancer diagnosis, age 80 years, death, or December 31, 2006, whichever occurred first.

We compared characteristics of recipients with and without lip cancer and with low versus high initial immunosuppressive dose using Student *t* tests, Wilcoxon rank sum tests, Pearson χ^2 tests, or Fisher exact tests as appropriate.

We applied 3 approaches to modeling the effect of immunosuppression. We first tested a time-dependent binary variable for the current receipt of each immunosuppressive agent. Second, we tested a time-dependent continuous variable for the current daily dose of each immunosuppressive agent. Third, to capture the overall dose of immunosuppressive therapy, we modeled the mean dose of each immunosuppressive agent during follow-up, calculated as the sum of doses at each follow-up time