Cancer Incidence in Immunocompromised Patients

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INTRODUCTION

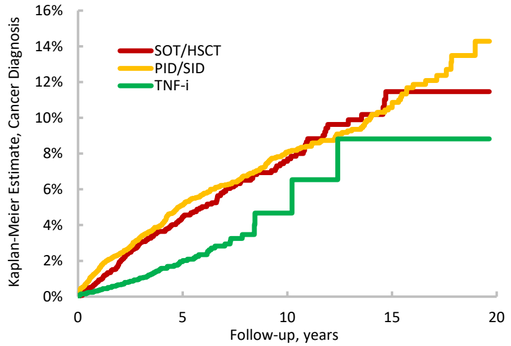
- Diminished immune defense plays an important role in cancer development.[1]
- The risk of cancer may differ by underlying cause/degree of immunosuppression.[2,3,4]
- Identifying individuals with elevated cancer risk can inform strategies for early cancer detection.
- Early detection of cancer has demonstrated benefits of improving prognosis, reducing long-term complexity of care, morbidity, mortality, and financial burden.[5]
- In the US, guideline recommended cancer screening tests are limited to only five cancer types.[6]
- Emerging multi-cancer early detection (MCED) tests can detect a variety of cancer types with a single blood draw.[7]
- Individuals at an elevated risk of cancer may benefit from MCED tests in addition to guideline recommended cancer screening.

OBJECTIVE

- This study aims to understand cancer incidence and potential risk factors in three patient groups:
  - Receipt of solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT)
  - Diagnosis of primary or secondary immunodeficiency disorder (PID/SID)
  - Receipt of tumor necrosis factor inhibitor (TNF-i) therapy.

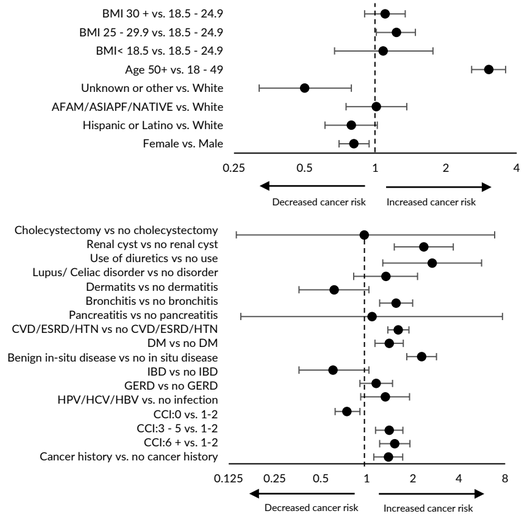
KEY RESULTS: PATIENTS WITH PRIMARY OR SECONDARY IMMUNODEFICIENCY OR TRANSPLANT DEMONSTRATED INCREASED CANCER RISK VERSUS PATIENTS RECEIVING TNF-i

Figure 1: Kaplan-Meier analysis of cancer incidence rate in risk cohorts



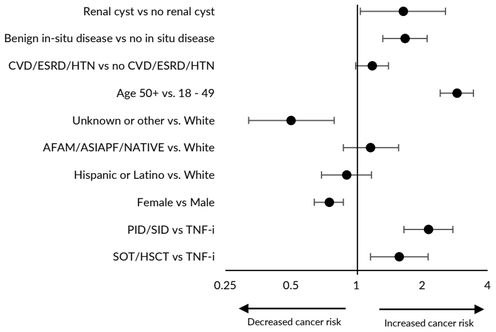
- Based on the Kaplan-Meier analysis (**Figure 1**), the estimated cumulative incidences at 5 year and full follow-up were 4.44% and 11.47% for the SOT/HSCT, 5.11% and 14.28% for the PID/SID, and 1.95% and 8.82% for the TNF-i cohort, respectively.
- In the SOT/HSCT cohort, GI cancer (14.3%) was the most common newly diagnosed cancer followed by cancer of hematopoietic system and skin cancer (12.4% each). In the PID/SID cohort, cancer of hematopoietic system was predominant (22.3%) followed by GI (16.8%) and skin cancer (14.2%). In the TNF-i cohort, cancer of reproductive system (17.4%) was the most common followed by breast cancer (15.9%).

Figure 2. Univariate hazard ratio of covariates on cancer risk for overall cohort



AFAM, African American; ASIAPF, Asian/Pacific Islander; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; CVD, Cardiovascular disease; DM, Diabetes Mellitus; ESRD, End stage renal disease; GERD, Gastroesophageal Reflux Disease; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HPV, Human Papilloma Virus; HTN, Hypertension; IBD, Inflammatory Bowel Disease; Native, Native American.

Figure 3: Multivariable model of cancer risk by risk cohort



Analysis was done using the Cox proportional hazard regression model.
AFAM, African American; ASIAPF, Asian/ Pacific Islander; Native, Native American

- The univariate hazard ratio estimates showed higher risk of cancer with age ≥50 years, BMI 25-29.9, benign in-situ disease, bronchitis, cardiovascular disease/ hypertension/end stage renal disease (CVD/HTN/ESRD), CCI ≥3, diabetes, diuretic use, history of prior cancer, and renal cyst. (**Figure 2**)
- Higher risk of cancer was observed in patients with SOT/HSCT and PID/SID compared to TNF-i cohort when controlling for age, gender, race/ethnicity, and significant clinical comorbidities. (**Figure 3**)
- Age ≥50 years, male gender, white race, presence of benign in-situ disease, and renal cyst were additional factors impacting cancer risk.

DISCUSSION

- Cancer incidence rate in SOT/HSCT and PID/SID cohort was almost twice as high as the age-adjusted cancer incidence (4.02 cases per 1000 person years) in the region.[8]
- Similar trends in the escalation of cancer risk among transplant patients have been reported in the literature.[2]
- The cancer risk among patients with PID/SID is higher than previous findings,[9] potentially due to heterogeneity in causes of immunodeficiency within the PID/SID cohort.
- Consistent with trends reported in the literature,[10] age was also found to be associated with cancer risk, with an effect size consistent across cohorts.
- A history of benign or in-situ growth was associated with an increased cancer risk in the overall cohort and within the PID/SID and SOT/HSCT cohorts.

CONCLUSION

- The risk of cancer varies among immunocompromised patients with higher incidences of cancer associated with patients in the PID/SID or SOT/HSCT cohorts compared to the TNF-i cohort.
- Factors such as age, and concurrent comorbidities (benign in-situ disease, renal cyst) demonstrated an association with cancer risk.
- Patients with PID/SID or SOT/HSCT may serve as an appropriate target population for early cancer detection strategies.
- Economic models and pragmatic trials can help delineate the value of early cancer detection strategies in individuals with elevated risk of cancer, such as immunocompromised patients.

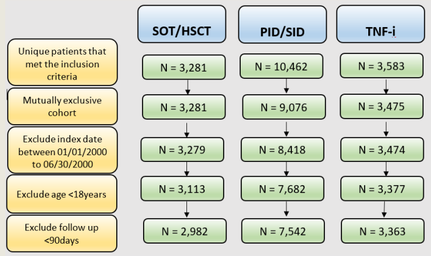
Authors' Contributions

All authors contributed to and approved the content.

METHODS

- This was a retrospective observational cohort study using data from both the University of Utah Electronic Data Warehouse (EDW) and the Huntsman Cancer Institute Tumor Registry (HCI-TR).
- Eligible patients included aged ≥18 years (with or without baseline cancer) with SOT/HSCT, PID/SID, or ≥3 months of TNF-i therapy between 7/1/2000 and 2/28/2018 with at least 90 days of follow-up post-index.
- The date of transplant, diagnosis of PID/SID, or first TNF-i medication order date was defined as the index date. Baseline demographics and risk factors for cancer were collected in the 180-day pre-index period. Follow-up ended at cancer diagnosis, last follow-up visit, death, or end of study period (2/28/2020).
- A Cox-proportional hazard regression model with a forward variable selection process (p<0.2) was used to adjust for risk factors known to increase the risk of cancer. Descriptive statistics were used to describe the baseline and clinical characteristics; ANOVA (continuous variable) and Chi-square/Fisher's Exact test (categorical variable) were used for statistical comparison.

Figure 4 . Flow diagram of cohort identification



- In total, 13,887 patients were included in the analysis; 2,982 patients under the SOT/HSCT cohort, 7,542 patients under the PID/SID cohort, and 3,363 patients under the TNF-i cohort. (**Figure 4**)

SUPPORTING DATA

Baseline characteristics across three risk cohorts

- The proportion of males was higher in the SOT/HSCT (62.5%), and PID/SID (54.2%) cohorts compared to the TNF-i cohort (37.2%).
- Mean age (SD): 46.8 (15) - 50.3 (18.2) years; proportion of patients with age ≥65 years ranged from 12.3-25.7%.
- Most of the patients were white (72.3-84.8%), followed by Hispanic/Latino (7.4-11.5%).
- Mean BMI (SD): 27.7 (7)- 29 (7.6). More than a third of patients in the SOT/HSCT and TNF-i cohort had a BMI ≥30; a normal BMI (18.5-24.9) was observed in 35.8% of the PID/SID cohort.
- Most patients (42%) in the SOT/HSCT cohort had a CCI score of 3-5; 0 in the PID/SID cohort (51.7%), and 1-2 in the TNF-i cohort (46.9%).
- Prior history of cancer was observed in 39% of patients in the SOT/HSCT cohort, followed by 8% in the PID/SID cohort.
- The most common baseline cancer in the SOT/HSCT (25%) and PID/SID (3.2%) cohort was cancer involving hematopoietic system while in the TNF-i cohort more skin, breast, head and neck cancer patients (14%) were identified.
- Hypertension (HTN)/ Cardiovascular disease (CVD)/ End Stage Renal Disease (ESRD), and Diabetes (DM) were the most common comorbidities observed in all three cohorts.
- The median follow-up period (IQR) was 5.5 years (3.0 - 9.4), 6.2 years (3.7 - 10.0), and 4.4 years (3.2 - 6.9) for the SOT/HSCT, PID/SID, and TNF-i cohorts, respectively.

LIMITATIONS

- Patient characteristics differed significantly between the cohorts, potentially complicating comparisons between the groups of patients. Nevertheless, covariates that were potentially confounding factors were controlled for in our analysis.
- In our covariate analyses, differences in the size of the cohorts may affect the strength of the associations observed.
- Findings of our research should be considered in the context of the retrospective observational research design, which is subject to misclassification due to the coding, incomplete records, and unobserved confounders.
- Because our research was limited to single-center, findings may not be generalizable to other sites/regions.

DISCLOSURES

Study funded by GRAIL, LLC, a subsidiary of Illumina, Inc. KCC and BMW are employees of GRAIL, LLC.

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