MedStar Health Research Institute

Immune-Related Adverse Events of Immune Checkpoint Inhibitors and Association with Overall Survival

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BACKGROUND

Emergence of immune checkpoint inhibitors (ICPi) has revolutionized standard of care treatment in a wide spectrum of cancer subtypes resulting in increased progression-free-survival and overall survival.[1] These agents up regulate activity of the immune system by blocking intrinsic down regulators of immunity such as CTLA-4 and PD-1.[1] This amplified immune activity can also result in off target autoimmune inflammation of healthy organs resulting in immune-related adverse effects (irAE). Various mechanisms contribute to the irAE affecting several organ systems, with effect on endocrine glands noted as one of the most common irAE, as well as arthralgias and vasculitis.[1] Correlation with the development of these adverse effects on outcomes is controversial, however, there is a growing body of evidence that the development of these adverse events may be associated with improved outcomes [(1-5)].

A preliminary study from our group has addressed this issue with a systematic literature review and meta-analysis (*Abstract submitted to ASCO 2019*)[6]. We have performed a systematic literature review within PubMed and EMBASE databases. Search terms included “durvalumab”, “atezolizumab”, “nivolumab”, “pembrolizumab”, “ipilimumab”, “head & neck cancer”, “lung cancer.” Studies published before September 2018 were included. The search was limited to randomized controlled trials (RCTs) phase III written in English. Data was extracted about patient characteristics, interventions, overall survival (OS), progression free survival (PFS), and endocrine irAEs. Summary hazard ratio (HR) and 95% confidence interval was calculated using the software Comprehensive Meta-Analysis and a scatter plot was generated. Our meta-analysis included twelve RCTs comprising 7060 patients; 3815 used an ICPi (treatment arm). The mean follow-up was 12.2 months ± 7.1 SD. The survival rate of the treatment arm was enhanced (HR, 0.75; 95% CI, 0.70-0.80), compared to the alternate arm. Similarly, the PFS of the treatment arm was improved (HR, 0.77; 95% CI, 0.72-0.81) but with a higher incidence of endocrine irAEs. The most common endocrine irAE reported was hypothyroidism; 193 patients in the treatment arm versus 29 in the alternate arm ($p<0.001$); grade 3/4 AE was observed in 10 patients versus 1 patient, respectively. Other endocrine irAEs were reported in 168 patients in the treatment arm versus 26 patients in the alternate arm ($p<0.001$); grade 3/4 AEs were observed in 28 patients versus 3

patients, respectively. The prevalence of endocrine irAEs in this meta-analysis was 9%. A significant positive correlation between endocrine irAEs and OS was observed (p=0.019). However, a study at individual patient level data would provide better evidence. We concluded that immune checkpoint inhibitors are powerful tools in the treatment of cancer. There is evidence of improved overall survival in patients who developed endocrine irAEs. Further studies are needed to correlate the development of irAEs and OS advantage in individual level data.

HYPOTHESIS

We hypothesize that the development of immune-related adverse events (irAEs) is positively correlated with outcomes in patients treated with immune checkpoint inhibitors (ICPi).

We intend to identify if specific irAEs carried more prognostic significance on the overall survival across different tumor types, as well as differences in overall survival based on gender, severity of side effects based on the percentage of PD-L1 expression, onset (early vs late) and degree (grade 1-2 vs 3-4) of adverse events. We hypothesize that the development of irAEs can be used as a surrogate marker of response to therapy.

OBJECTIVE OF THE STUDY

To retrospectively review data from all patients with a stage IV solid malignancy who have used an immune checkpoint inhibitor.

Primary aim

To identify incidence of any immune-related adverse events (irAE) in these patients, and to demonstrate correlation between the incidence of irAE and overall survival.

Secondary aim

To sub-stratify based on gender, cancer subtypes, line of treatment, percentage of PD-L1 expression, time of onset of irAE and severity of irAE, and identify differences in overall survival among these subgroups.

STUDY DESIGN: METHODS AND PROCEDURES

We will perform a retrospective review of electronic medical records in Medstar Washington Cancer Institute. We will use EMR systems, such as Centricity, Amalga, Aria and MedConnect to identify the subjects. Data tracking, data entry and storage will comply with HIPAA regulations. The records will be reviewed from January 2013 to January 2018. We expect to retrieve around 300 results corresponding patients with stage IV solid malignancy using an immune checkpoint inhibitor at MWHC in this range of time. Data collected from the records will include age, gender, date of cancer diagnosis, type of cancer, staging, sites of metastasis, line of treatment, molecular markers, percentage of PD-L1 expression, date of start of ICPi, date of first reported irAE, description of irAE, severity of irAE based on CTCAE v4.0 grading[7], date of death (if applicable). Laboratory data and imaging studies (ultrasound studies, nuclear medicine scans, CT scans, MRI, PET-CT) necessary to characterize immune related adverse events will also be documented.

Patients meeting the following eligibility criteria will be included in the study:

Inclusion Criteria

All patients with stage IV solid malignancy who have been initiated on an immune checkpoint inhibitor (Pembrolizumab, Atezolizumab, Durvalumab, or Nivolumab).

Exclusion Criteria

1. Patients with hematological malignancies.
2. Patients with solid malignancies, stage I-III.
3. Patients treated in combination with CTL4 inhibitors such as Ipilimumab.

Subject Recruitment and Screening

Recruitment will be done initially by retrospective review in conjunction with the HIPAA waiver. Subjects will be screened according to the inclusion criteria.

IRB Approval and HIPAA waiver

The study will start upon IRB approval of all documents including the protocol and HIPAA waiver.

PATIENT DATA

An Excel spreadsheet will be created to organize pertinent patient data, including:

- Age;
- Gender;
- Date of cancer diagnosis, type of cancer, staging, sites of metastasis;
- Molecular markers, percentage of PD-L1 expression;
- Line of treatment, date of start of ICPi;
- Date of first reported irAE, description of irAE, severity of irAE;
- Laboratory tests, including hepatitis panel, endocrine tests (thyroid function tests, anti-thyroid antibodies, cortisol), rheumatology tests (RF, CCP, ANCA, ANA, SSA/SSB), among other routine lab tests;
- Imaging studies: ultrasound studies, nuclear medicine scans, CT scans, MRI, PET-CTs;
- Date of death (if applicable).

STATISTICAL ANALYSIS PLAN

Descriptive statistics will be reported as mean ± standard deviation, and confidence intervals will be computed as two-tailed using 95% coverage. Categorical variables will be reported as frequencies and proportions. Statistical analysis will be done to determine relationship between irAEs and overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier methods and Cox proportional hazard regression.

Statistical analysis will be conducted by the statisticians in the Department of Biostatistics and Biomedical Informatics of MHRI.

DATA MANAGEMENT AND RECORD KEEPING

Confidentiality

We are requesting waiver of HIPAA authorization to perform this study. As a retrospective study, we need access to patients' medical records and it is impractical or impossible to obtain authorization from each individual. Access to PHI, including DOB, Date of Service,

clinical records, pathology, laboratory and imaging data, is required so as to perform this study.

We will protect the identifiers from improper use and disclosure. The main identified spreadsheet will be password-protected on a secure network (MedStar computer with limited access). Secondary spreadsheets will be created in which all the PHI is replaced by a study code. At the end of the study all spreadsheets will be permanently deleted and any eventually printed document containing PHI will be shredded.

The Principal Investigator will ensure that subjects' anonymity is maintained. Subjects will not be identified in any reports on this study. All records will be kept confidential to the extent required by federal, state and local law. Protected health information will not be reused or disclosed to any other person or entity except as required by law or for authorized oversight of the research study.

Study Documentation and Storage

The Principal Investigator is responsible for maintaining a comprehensive and centralized filling system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the MHRI, IRB, FDA, and/or applicable regulatory authorities.

Data will be stored in a HIPAA compliant manner, at MedStar servers.

In addition, all original submission documentation will be maintained and be readily available at the IRB system. All essential documentation should be retained by the institution for the same period of time required for medical records retention. No study document should be destroyed without prior written agreement between the MHRI and the Principal Investigator. Should the investigator wish to assign the study records to another party or move them to another location, MHRI must be notified in writing of the new responsible person and/or the new location.

REFERENCES

1. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. New England Journal of Medicine. 2018 Jan 11;378(2):158-68.
2. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, Luiten RM. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. 2015 Mar 1;33(7):773-81.
3. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clinical Cancer Research. 2016 Feb 15;22(4):886-94.
4. Kim HI, Kim M, Lee SH, Park SY, Kim YN, Kim H, Jeon MJ, Kim TY, Kim SW, Kim WB, Kim SW. Development of thyroid dysfunction is associated with clinical response to PD-1 blockade treatment in patients with advanced non-small cell lung cancer. Oncoimmunology. 2018 Jan 2;7(1):e1375642.
5. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, Rodriguez C, Cambridge L, Rizvi H, Wolchok JD, Merghoub T. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Annals of Oncology. 2017 Mar 1;28(3):583-9.
6. Gomes-Lima CJ, Kwagyan J, King F, Fernandez SJ, Burman KD, Veytsman I. A comprehensive meta-analysis of endocrine immune-related adverse events of immune checkpoint inhibitors and outcomes in head and neck cancer and lung cancer. J Clin Oncol 37, 2019 (suppl; abstr e14096).
7. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.0.