World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:15, No:10, 2021

Risk of Mortality and Spectrum of Second Primary Malignancies in Mantle Cell Lymphoma before and after Ibrutinib Approval: A Population-Based Study

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Abstract : Background: Mantle cell lymphoma (MCL) is one of the mature B cell non-Hodgkin lymphomas (NHL). The course of MCL is moderately aggressive and variable, and it has median overall survival of 8 to 10 years. Ibrutinib, a Bruton's tyrosine kinase inhibitor, was approved by the United States (US) Food and Drug Administration in November of 2013 for the treatment of MCL patients who have received at least one prior therapy. In this study, we aimed to evaluate whether there has been a change in survival and patterns of second primary malignancies (SPMs) among the MCL population in the US after ibrutinib approval. Methods: Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-18, we conducted a retrospective study with patients diagnosed with MCL (ICD-0-3 code 9673/3) between 2007 and 2018. We divided patients into two six-year cohorts, pre-ibrutinib approval (2007-2012) and post-ibrutinib approval (2013-2018), and compared relative survival rates (RSRs) and standardized incidence ratios (SIRs) of SPMs between cohorts. Results: We included 9,257 patients diagnosed with MCL between 2007 and 2018 in the SEER-18 survival and SIR registries. Of these, 4,205 (45%) patients were included in the pre-ibrutinib cohort, and 5052 (55%) patients were included in the post-ibrutinib cohort. The median follow-up duration for the pre-ibrutinib cohort was 54 months (range 0 to 143 months), and the post-ibrutinib cohort was 20 months (range 0 to 71 months). There was a significant difference in the five-year RSRs between pre-ibrutinib and post-ibrutinib cohorts (57.5% vs. 62.6%, $p < 0.005$). Out of the 9,257 patients diagnosed with MCL, 920 developed SPMs. A higher proportion of SPMs occurred in the post-ibrutinib cohort (63%) when compared with the pre-ibrutinib cohort (37%). Non-hematological malignancies comprised most of all SPMs. A higher incidence of non-hematological malignancies occurred in the post-ibrutinib cohort (SIR 1.42, 95% CI 1.29 to 1.56) when compared with the pre-ibrutinib cohort (SIR 1.14, 95% CI 1 to 1.3). There was a statistically significant increase in the incidence of cancers of the respiratory tract (SIR 1.77, 95% CI 1.43 to 2.18), urinary tract (SIR 1.61, 95% CI 1.23 to 2.06) when compared with other non-hematological malignancies in post-ibrutinib cohort. Conclusions: Our study results suggest the relative survival rates have increased since the approval of ibrutinib for mantle cell lymphoma patients. Additionally, for some unclear reasons, the incidence of SPM's (non-hematological malignancies), mainly cancers of the respiratory tract, urinary tract, have increased in the six years following the approval of ibrutinib. Further studies should be conducted to determine the cause of these findings.

Keywords : mantle cell lymphoma, Ibrutinib, relative survival analysis, secondary primary cancers
Conference Title : ICHBD 2021 : International Conference on Hematology and Blood Disease
Conference Location : New York, United States
Conference Dates : October 07-08, 2021