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Predicting Response to Immune Checkpoint Inhibitor Therapy: Emerging Role for Artificial Intelligence?

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Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic landscape for patients with cancer, leading to improved clinical outcomes in numerous malignancies with historically poor prognoses. However, only a subset of patients will benefit from treatment with ICIs. Due to disease heterogeneity and lack of viable targets, development of predictive biomarkers to select which patients will benefit the most has been largely disappointing. Previously, we identified clinical factors associated with outcome in solid tumor patients treated with ICIs, including those with good performance status and family history of cancer. However, such retrospective analysis from a single institutional is limiting, and there is an urgent need for more efficient and comprehensive methodology. Fast forwarding to present day, artificial intelligence has gained greater momentum as an avenue for improving the diagnosis and treatment of cancer. Here, we review recent advances and the potential role of applying artificial intelligence to predict ICI treatment outcomes.

Keywords: *Immune checkpoint inhibitors; Cancer; Artificial Intelligence; Biomarkers*

Introduction

The use of immunotherapy to treat malignancies was first explored in 1891 by William Bradley Coley, who injected streptococcal organisms to induce an infection, and indirectly treated bone cancer [1]. In 1977, Lloyd J. Old postulated that the immune system is able to distinguish cancer cells from normal cells as cancer cells are inherently unique in nature [2]. These pioneer concepts paved the way to the development of cancer immunotherapy as a standard therapeutic approach, with the development of ICIs as a key turning point to improving cancer outcomes in the modern era.

ICIs are monoclonal antibodies that indirectly trigger the immune system to target cancer cells by either stimulating activating receptors or blocking inhibitory receptors [3]. For example, as a key component of self-tolerance, cytotoxic T-lymphocye-associated antigen 4 (CTLA-4) downregulates the immune response to prevent attack of host cells [4]. Ipilimumab, a monoclonal antibody blocking CTLA-4, was the first ICI to be approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma [5]. Shortly thereafter, monoclonal antibodies against programmed cell death protein 1 (PD-1) or its ligand (PD-L1) showed promising results in a myriad of cancer types. PD-L1 can be found on the surface of some tumor cells while PD-1 is found on the surface of T-lymphocytes. Inhibitory signals emitted by the formation of the PD1/PD-L1 complex suppress the proliferation and activation of cytotoxic T-lymphocytes [6,7]. This mechanism allows for cancer cells expressing PD1 to evade the immune response.

While ICIs have exhibited promising results by reducing tumor burden and improving survival rates, only about one-third of patients exhibit a durable response [8]. Predicting response to ICIs has proven challenging due to the complex nature of the interaction between tumor microenvironment and host immune response. Currently, PD-L1, tumor mutational burden (TMB), and microsatellite instability (MSI) are clinically validated biomarkers in some cancer types to predict response to ICIs, but unfortunately, they are far from perfect. Recent developments have explored the roles of other biomarkers, including tumor infiltrating lymphocytes, gut microbiota, and POLE mutations outside the exonuclease domain [9-11]. However, their applicability to date remains limited.

Better understanding of what clinical factors may predict response

to ICIs is critical, as it may be the basis for further investigation of the underlying molecular rationale. In a single-institution retrospective study of 297 solid tumor patients treated with ICIs, we found that preserved performance status of ECOG 0-1 and family history of cancer were associated with improved response to ICIs [12]. The presence of bone metastasis was associated with worse response to ICIs. Other clinical characteristics such as age, race, sex, smoking history, and comorbidities were not significantly associated with differences in response to ICIs. However, given the large number of clinical variables in this dataset, the analysis required enormous human labor to appropriately capture and analyze, and additionally there are important variables we could not accurately capture. We urgently need more efficient methodology to perform such analysis going forward.

As seen in other fields, artificial intelligence (AI) has the potential to advance medical research and provide a platform for more comprehensive and effective investigation. For instance, AI can more effectively capture data from electronic medical record, such as imaging and laboratory results, to streamline research processes, and to ensure data accuracy. For both radiology and pathology, AI (machine and deep learning) has demonstrated the potential to improve screening, detection, and diagnosis of cancer [13-16]. Although to date, there is limited evidence to support using AI in predicting therapeutic response, recent reports of its application provide proof of concept that such strategies are on the horizon.

Deep and Machine Learning: Pathology and Clinical Models

Several studies have investigated whether deep learning can predict cancer immunotherapy response. Using a multi-center, international retrospective cohort of 2799 patients with gastric cancer, Jiang Y, et al. (2023) trained and validated a biology-guided deep learning model that utilized diagnostic CT images to classify tumor microenvironment (TME) and predict prognosis [17]. Immunohistochemistry evaluation of established immune and stromal markers was used to define four predicted TME classes. In an independent cohort of 303 patients with advanced gastric cancer, this deep learning model of TME classes was able to predict response to PD1 inhibitors better than PD-L1 expression, and a significantly higher accuracy for response prediction was observed using a simple interpretable model that combined TME classes and PD-L1 expression.

Li Y, et al. (2022) used a retrospective cohort of 7868 non-small cell lung cancer (NSCLC) patients who received first line ICI therapy to develop a machine learning-based survival model, which achieved C-indices of 0.672 and 0.612 for overall survival (OS) and progression-free survival (PFS), respectively [18]. Significant predictors of OS and PFS were identified using explain-ability techniques and these predictors, such as ECOG, PD-L1 expression levels, and albumin, aligned with published literature and what has been observed in clinical practice. Wu Y, et al. (2023) used machine-learning algorithms to develop prediction models using a cohort of 2538 patients with NSCLC, transitional cell carcinoma, or renal cell carcinoma who received atezolizumab in 8 different clinical trials [19]. With the best overall predictive performance, the random forest (RF) model had a receiver operating characteristic curve (AUC) value of 0.786 (95% CI: 0.754-0.818) for predicting mortality [19]. Using a retrospective cohort of 976 patients with metastatic, EGFR/ALK negative NSCLC treated with ICIs, Saad MB, et al. (2023) developed an ensemble deep learning model based on pretreatment CTs to predict survival outcomes after ICI treatment [20]. The Deep-CT model demonstrated better prediction performance than risk factors like PD-L1 expression, smoking status, and histology, especially when integrated with these risk factors into a composite model [20]. This composite model had an improved OS C-index of 0.75 compared to the clinical model with a C-index of 0.7020. Although further validation is required, these findings serve as early evidence that deep machine learning can indeed improve prognostication and prediction of ICI response [20].

Deep and Machine Learning: Radiomic Models

Radiomics involves the use of mathematical methods to extract measurable quantitative features from imaging under the hypothesis that such features correlate to a tumor's biological properties [21]. Several studies have developed radiomics-based models intended to predict response to ICI therapy. In a multicenter study, Zhao J, et al. (2023) used a retrospective cohort of 240 patients with advanced breast cancer to develop and validate a radiomics-based model to predict ICI response [22]. Clinicopathologic features and pretreatment contrast-enhanced CT imaging from these patients were assigned to training and independent validation cohorts [22]. The radiomics model demonstrated significantly better performance than the clinical model with an AUC of 0.994 (95% CI: 0.988 to 1.000) in the training and 0.920 (95% CI: 0.824 to 1.000) in the validation set compared to an AUC of 0.672 for training and 0.634 for validation set in the clinical model. With significant differences in PFS in both the training and validation sets, this radiomics model was able to stratify patients receiving ICIs into high- and low-risk groups. These findings show the promising potential of using such radiomics-based models in predicting treatment response to ICIs.

Ventura D, et al. (2023) developed a model of radiomics features used to classify response and overall progression in 44 patients with advanced NSCLC who received first-line ICIs [23]. PET-positive tumor volumes of all lesions were segmented to extract baseline PET and CT data from which radiomics features were extracted. They found an AUC of 0.69 for predicting response and 0.75 for predicting overall progression. Zhu Z, et al. (2023) conducted a single-center retrospective study in which they

developed a pre-treatment CT-based predictive radiomic model based on a cohort of 185 patients with advanced lung cancer and cross-validated it in a test cohort of 48 patients [24]. An attention-based multiple-instance learning model was used to weight radiomic features that were extracted from a number of intrapulmonary lesions. Machine learning-based predictive models were then developed using both radiomic and clinical features. Kaplan-Meier analysis of the radiomic-based predictive models clearly stratified patients as having either classifier-predicted durable clinical benefit or non-durable clinical benefit (HR = 2.40-2.95, $p < 0.05$). By integrating clinical features such as age, clinical stage, presence of bone metastasis, line of therapy, and the use of pembrolizumab, the performance of the radiomic-only model was significantly enhanced. Tonneau M, et al. (2023) used a multi-center cohort of 642 advanced NSCLC patients treated with ICIs to extract radiomics features from pre-treatment imaging [25]. This cohort was divided into a discovery cohort of 512 patients and a validation cohort of 130 patients. The predictive value of radiomics, PD-L1 expression, and clinical variables, such as age, ECOG status, treatment line, and smoking history, was estimated using cross-validated multivariable models. When using only clinicopathologic features to define standard-of-care prognostic scores, a combination of clinical factors and PD-L1 expression served as the best clinical prognostic factor for PFS at 6 months with an AUC of 0.66 (95% CI: 0.61 to 0.70) in the discovery cohort and 0.62 (95% CI: 0.53 to 0.72) in the validation cohort as compared to clinical factors alone or PD-L1 expression alone. After CT imaging harmonization and machine learning generalization, a risk prediction model combining clinical factors and deep radiomics was found to be generalizable by reaching an AUC of 0.67 and 0.63 in the discovery and validation cohorts respectively. These findings support the potential of machine and deep learning radiomics as a future method of predicting response to ICIs [26].

Future Directions

Recent advances in AI application to predict therapeutic outcomes suggest there is potential for an accelerated path to better understanding how to select the best candidates for ICI treatment going forward. Future AI models should be multimodal in nature, encompassing information from various sources of clinical and biomarker data from large datasets, to maximize the predictive potential of such models (Figure 1). With further clinical validation, such precision AI models may aide everyday clinical practice by predicting optimal treatment strategies, leading to better patient outcomes.

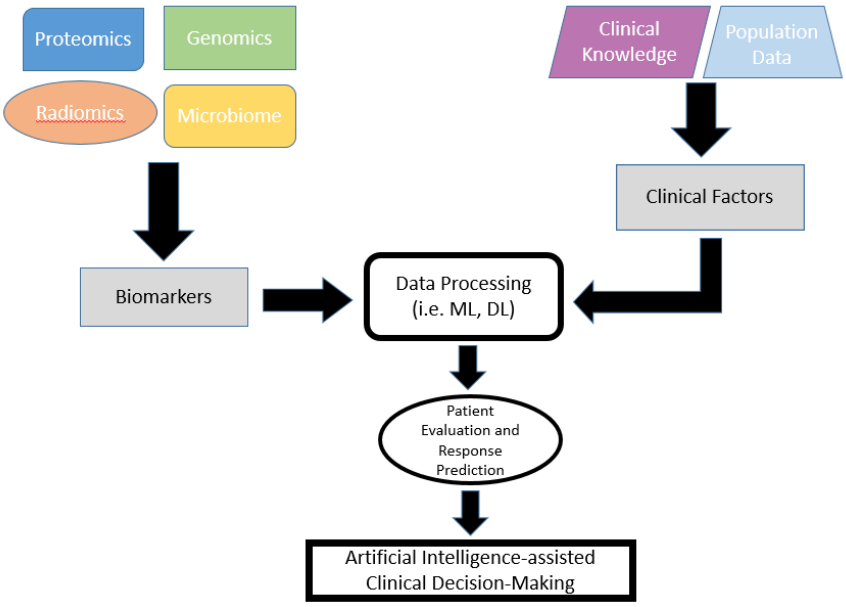

Figure 1: Framework for use of artificial intelligence to predict response to immune checkpoint inhibitors for clinical decision-making.

Conclusion

While ICIs have changed the therapeutic landscape for many patients with cancer, predicting which patients will truly benefit remains a significant challenge. While clinical factors and biomarkers have been individually identified for ICI treatment selection in some cancers, they generally lack the high sensitivity and specificity for broader implication. The potential of early AI application witnessed to date has been promising, and should further optimize ICI selection for cancer patients in the near future.

Conflict of Interest

The authors declare that they have no conflict of interest.

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