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AUTHOR'S VIEW

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Precision immunity: Immunoscore and neoadjuvant treatment in bladder cancer

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ABSTRACT

This review details the clinical utility of Immunoscore, measuring the immune response to cancer within the tumor microenvironment, in bladder cancer. Immunoscore was recently introduced into ESMO Clinical Practice Guidelines for gastrointestinal cancer and into the WHO classification of the Digestive System Tumors. In muscle-invasive bladder cancer (MIBC), the standard-of-care treatment is neo-adjuvant chemotherapy and cystectomy. However, only 50% of the patients are still alive at 5 years. The degree of histologic response positively correlated with Immunoscore and patients at lower risk of relapse or death were associated with a high-Immunoscore. Immunoscore is also predicting response to neoadjuvant chemotherapy-based treatment in several indications. This paves the way for the use of Immunoscore in clinical practice not only in gastrointestinal tumors but also in bladder cancer, and beyond.

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The goal of cancer therapies is to enable patients to live better and/or longer. There is only 50% of the patients with muscle-invasive bladder cancer (MIBC) alive after standard-of-care treatment with neoadjuvant chemotherapy (NAC) and cystectomy.[1] Two major clinical prognostic factors are recognized, nodal involvement and achievement of a pathological complete response (pCR) after neoadjuvant treatment. Approximately 60–75% patients have residual tumor after NAC. However, there is currently no validated tumor biomarker to predict chemotherapy sensitivity to guide treatment decision

The different subpopulations of immune cells are associated with variable prognostic significance.[2,3] Multiple analyses and meta-analyses have highlighted the role of particular subpopulation of adaptive immune cells. In particular, T lymphocytes and cytotoxic T-cells have a major influence on patient survival.[2–6] Recently, the international consortium of the Consensus Immunoscore validated the prediction of clinical outcome and response to chemotherapy.[7–9] Multiple studies and analysis were performed to validate the analytical performance of Immunoscore.[9,10] Immunoscore can provide new information on host-defense against the tumor, which is an essential element in the success of immunotherapy and of any cancer therapy mobilizing the immune response.[11,12]

We investigated whether Immunoscore performed on urothelial carcinoma with localized muscle-invasive bladder cancer (MIBC) tumor samples could predict response to neoadjuvant chemotherapy and survival outcome.[13] We evaluated Immunoscore in 117 patients with localized MIBC from 6 centers in France and in Greece. High-Immunoscore was significantly associated with pathologic complete response (pCR) (P = .0096). High-Immunoscore was more frequent in patients with pCR, compared to patients without pCR. Furthermore, high-Immunoscore was significantly associated with a prolonged time to recurrence (P = .01). This study revealed a significant prognostic value of Immunoscore and a predictive role of Immunoscore in MIBC patients undergoing neoadjuvant chemotherapy. This study has important potential therapeutic implications that warrant further prospective validation.

Since the prognosis of localized muscle-invasive bladder cancer is poor, and since prognostic and predictive markers of response to treatment are lacking, it is essential to propose novel precision medicine-based treatments to patients. We found that Immunoscore predicts response to neoadjuvant chemotherapy and survival (Figure 1).

Major validations of the prognostic and predictive values of Immunoscore in colon cancer were published.[2–6,14,15] Recently, the 2020 ESMO Clinical Practice Guidelines for colon cancer included Immunoscore to refine the prognosis and thus adjust the chemotherapy decision-making process. Furthermore, the introduction into the latest (5th) edition of the WHO Digestive System Tumors of the immune response, as measured by Immunoscore, as essential and desirable diagnostic criteria for colorectal cancer. Immunoscore is a validated strong prognostic factor in colorectal cancer and a predictor to response to chemotherapy.[7,8] Importantly, in localized colorectal cancer, Immunoscore was found to be more efficient at stratifying patients' prognosis than TNM staging.[9] The immunosurveillance and the importance of the immune contexture of tumors have been demonstrated from pre-cancer to metastasis.[16–18]

The clinical utility of evaluating the immune response with Immunoscore now extends beyond colon cancer and has also a role in predicting response to neoadjuvant treatments. Thus, Immunoscore may facilitate a personalized treatment of

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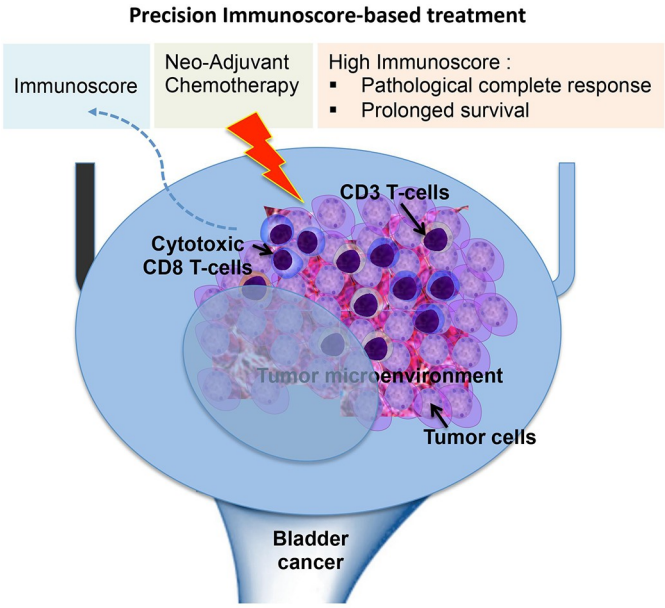

Figure 1. Illustration of a precision immunoscore-based neoadjuvant treatment approach.

bladder cancer. Patients with high-Immunoscore before neoadjuvant treatment were associated with pCR, and prolonged TTR and OS.

A specific predominant prognostic impact of one of the individual densities, quantified in the center of tumor (ct) or in the invasive margin (im), of either CD3-ct, CD3-im, CD8-ct and CD8-im were observed in different subtypes of bladder cancer. A combined consensus reproducible assay, such as Immunoscore, could be a more robust assay to perform across subtypes and clinical stages. Immunoscore efficiently allowed patient risk-stratification and prediction of response to neoadjuvant chemotherapy, which speaks to the clinical utility of Immunoscore for patient management. These results warrant further evaluation, which is underway, in prospective trials before being implemented in clinical routine.

The ultimate goal will be to stratify patients who will benefit most of the combination therapy, or of a monotherapy of either checkpoint inhibitors or chemotherapy. Checkpoint inhibitors and chemotherapy have important toxicities. Assessing the benefit-risk of each modality treatment in this curative setting is essential.

Surgery is associated with significant morbidity and impairment of the quality of life. Clinicians and patients are seeking alternatives to such radical resection. Radiochemotherapy is an acceptable alternative for organ-sparing surgery, in selected populations. However, this approach can only be considered in patients with favorable responses to chemotherapy. It is thus of utmost importance to have diagnostics biomarkers allowing to predict pCR in MIBC patients following neoadjuvant therapy. This would be a reasonable strategy for patients who desire organ preservation or are considered medically inoperable.

Neoadjuvant and Immunoscore across cancer types

High Immunoscore is associated with pCR to neoadjuvant chemotherapy and prolonged survival in multiple settings and cancer types. Immunoscore was evaluated on 579 patients from four different histologies. Indeed, we found that Immunoscore predicted response to neo-adjuvant treatment in urothelial carcinoma and muscle-invasive bladder cancer (n = 117),[13] in triple-negative breast cancer (n = 103),[19] in advanced Head and Neck cancer patients (n = 110),[20] and in locally advanced rectal cancer in two independent cohorts (n = 131, n = 118) (LARC).[21]

In a recent review, we discuss the Immunoscore and its probable universal characteristic as a prognostic factor across multiple cancers.[2] Thus, the Immunoscore is likely to provide a tumor agnostic method to define immune fitness of a given tumor and to characterize, with a consensus method, the hot-altered- and cold-immune tumors. Furthermore, Immunoscore could also predict response to certain therapies and in particular neoadjuvant chemotherapy-based treatments across multiple cancer types, and ultimately, help save the lives of patients with cancer.

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Declaration of interests

JG has patents associated with the immune prognostic biomarkers. JG is the co-founder of HalioDx biotech company. Immunoscore® a registered trademark from the National Institute of Health and Medical Research (INSERM) licensed to HalioDx.

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