Precision immunity: Immunoscore and neoadjuvant treatment in bladder cancer

Elise N. Nassif, Constance Thibault, Stéphane Oudard, and Jérôme Galon

Oncology Department, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, University of Paris, Paris, France; Laboratoire of Integrative Cancer Immunology, INSERM, Paris, France; Equipe Labellisée Ligue Contre le Cancer, Paris, France; Centre de Recherche des Cordeliers, Sorbonne Université, Université de Paris, Paris, France

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 neoadjuvant 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.

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.2,3 Recently, the international consortium of the Consensus Immunoscore validated the prediction of clinical outcome and response to chemotherapy.4–9 Multiple studies and analysis were performed to validate the analytical performance of Immunoscore.4,10 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...
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 neoadjuvant treatment in urothelial carcinoma and muscle-invasive bladder cancer (n = 117), in triple-negative breast cancer (n = 103), in advanced Head and Neck cancer patients (n = 110), and in locally advanced rectal cancer in two independent cohorts (n = 131, n = 118) (LARC).

In a recent review, we discuss the Immunoscore and its probable universal characteristic as a prognostic factor across multiple cancers. 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.

Acknowledgments

The authors thank the patients and their caregivers.

Funding

The work was supported by INSERM, AP-HP, University Paris Descartes, the Cancéropole Ile-de-France, the Cancer Research for Personalized Medicine (CARPEM), Paris Alliance of Cancer Research Institutes (PACRI), the LabEx Immuno-Oncology, the National Cancer Institute of France (INCa; ref 2012-218), HalioDx for Immunoscore®, La Ligue Contre le Cancer, Association pour la Recherche contre le Cancer (ARC) and FONCER Contre le Cancer grant.

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.

References

1. Vale CL, Collaboration ABCAM-A. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48:202–205. doi:10.1016/j.euro.2005.04.006.
2. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat Rev Cancer. 2020. doi:10.1038/s41568-020-0285-7.
3. Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. Immunity. 2020;52:55–81. doi:10.1016/j.immuni.2019.12.018.
4. Galon J, Fox BA, Bifulco CB, Masucci G, Rau T, Botti G, Marincola FM, Ciliberto G, Pages F, Ascierto PA, et al. Immunoscore and immunoprofiling in cancer: an update from the melanoma and immunotherapy bridge 2015. J Transl Med. 2016;14:273. doi:10.1186/s12967-016-1029-z.
5. Kirilovsky A, Marliot F, El Sissy C, Haicheur N, Galon J, Pages F. Rational bases for the use of the immnoscore in routine clinical settings as a prognostic and predictive biomarker in cancer 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.
patients. Int Immunol. 2016:28:373–382. doi:10.1093/intimm/dsx021.
5. Pages F, Galon J, Fridman WH. The essential role of the in situ immune reaction in human colorectal cancer. J Leukoc Biol. 2008;84:981–987. doi:10.1189/jlb.1107773.
6. Mlecnik B, Bifulco C, Bindea G, Marliot F, Lugli A, Lee JJ, Zlobec I, Rau TT, Berger MD, Nagtegaal ID, et al. Multicenter international society for immunotherapy of cancer study of the consensus immunoscore for the prediction of survival and response to chemotherapy in stage III colon cancer. J Clin Oncol. 2020;38:JCO1903205. doi:10.1200/jco.19.03205.
7. Pages F, Andre T, Taieb J, Vernerey D, Henriques J, Borg C, Marliot F, Ben Jannet R, Louvet C, Mineur L, et al. Prognostic and predictive value of the Immunoscore in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France PRODIGE-GERCOR cohort study. Ann Oncol. 2020;31:921–929. doi:10.1016/j.annonc.2020.03.310.
8. Pages F, Mlecnik B, Marliot F, Bindea G, Ou FS, Bifulco C, Lugli A, Zlobec I, Rau TT, Berger MD, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. Lancet. 2018;391:2128–2139. doi:10.1016/S0140-6736(18)30789-X.
9. Marliot F, Chen X, Kirilovsky A, Sharrato T, El Sissy C, Batista L, Van den Eynde M, Haicheur-Adjouri N, Anitei MG, Musina AM, et al. Analytical validation of the immunoscore and its associated prognostic value in patients with colon cancer. J Immunother Cancer. 2020;8:e000272. doi:10.1136/jitc-2019-000272.
10. Stoll G, Enot D, Mlecnik B, Galon J, Zitvogel L, Kroemer G. Immune-related gene signatures predict the outcome of neo-adjuvant chemotherapy. Oncoimmunology. 2014;3:e27884. doi:10.4161/onci.27884.
11. Vacchelli E, Galluzzi L, Fridman WH, Galon J, Sautes-Fridman C, Tartour E, Kroemer G. Trial watch: chemotherapy with immunogenic cell death inducers. Oncoimmunology. 2012;1:179–188. doi:10.4161/onci.1.2.19026.
12. Nassif EF, Mlecnik B, Thibault C, Auvray M, Bruni D, Colau A, Compérat E, Bindea G, Catteau A, Fugon A, et al. The immunoscore in localized urothelial carcinoma treated with neoadjuvant chemotherapy: clinical significance for pathologic responses and overall survival. Cancers. 2021;13:494. doi:10.3390/cancers13030494.
13. Bindea G, Mlecnik B, Angell HK, Galon J. The immune landscape of human tumors: implications for cancer immunotherapy. Oncoimmunology. 2014;3:e27456. doi:10.4161/onci.27456.
14. Angelova M, Mlecnik B, Fridman WH, Galon J. The prognostic impact of anti-cancer immune response: a novel classification of cancer patients. Semin Immunopathol. 2011;33:335–340. doi:10.1007/s00281-011-0264-x.
15. Van den Eynde M, Mlecnik B, Fridman WH, Galon J. The link between the multiverse of immune microenvironments in metastases and the survival of colorectal cancer patients. Cancer Cell. 2018;34:1012–1026 e1013. doi:10.1016/j.ccell.2018.11.003.
16. Angell M, Mlecnik B, Vasaturo A, Bindea G, Fredriksen T, Lafontaine L, Buttard B, Morgand E, Bruni D, Jouret-Mourin, A. et al. Evolution of Metastases in Space and Time under Immune Selection. Cell. 2018;175:751–765 e716. doi:10.1016/j.cell.2018.09.018.
17. Mlecnik B, Angelova M, Vasaturo A, Beane J, Hijazi K, Anthoine G, Buttard B, Rothe F, Willard-Gallo K, Haller A, et al. Immune evasion before tumour invasion in early lung squamous carcinogenesis. Nature. 2019;571:570–575. doi:10.1038/s41586-019-1330-0.
18. Van den Eynde M, Mlecnik B, Bindea G, Fredriksen T, Church SE, Lafontaine L, Haicheur N, Marliot F, Angelova M, Vasaturo A, et al. The link between the multiverse of immune microenvironments in metastases and the survival of colorectal cancer patients. Cancer Cell. 2018;34:1012–1026 e1013. doi:10.1016/j.ccell.2018.11.003.
19. Rapoport BL, Galon J, Nayler S, Mlecnik B, Fugon A, Benn CA, Martel M, Cronje T, Smit T, Moosa F, et al. Tumour infiltrating lymphocytes in breast cancer: high levels of CD3, CD8 cells and Immunoscore (R) are associated with pathological CR in patients receiving neo-adjuvant chemotherapy. Ann Oncol. 2020;31:S31–S32. doi:10.1016/j.annonc.2020.03.180.
20. Mirghani H, Mure C, Mlecnik B, Hermitte F, Martel E, Casiraghi O, Iacob M, Even C, Galon J. High immunoscore is associated with good response to neo-adjuvant chemotherapy and prolonged survival in advanced head and neck cancer patients. Ann Oncol. 2019;30:452. doi:10.1093/annonc/mdz252.006.
21. El Sissy C, Kirilovsky A, Van den Eynde M, Musina AM, Anitei MG, Romero A, Marliot F, Junca A, Doyen J, Mlecnik B, et al. A diagnostic biopsy-adapted immunoscore predicts response to neo-adjuvant treatment and selects patients with rectal cancer eligible for a watch-and-wait strategy. Clin Cancer Res. 2020;26:5198–5207. doi:10.1158/1078-0432-ccr-20-0337.