Editorial

Prognostic value of tumor-infiltrating immune cells in patients with colorectal cancer

Ehsan Nazemalhosseini-Mojarad[1], Pedram Azimzadeh[1], Peter J.K. Kuppen[2]

[1]Gastroenterology and Liver Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Surgery, Leiden University Medical Center, Leiden, Netherlands

Correspondence to: Ehsan Nazemalhosseini-Mojarad. Gastroenterology and Liver Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: ehsanmojarad@gmail.com.

Submitted Jul 21, 2014. Accepted for publication Aug 06, 2014.
doi: 10.3978/j.issn.2224-4778.2014.08.07
View this article at: http://dx.doi.org/10.3978/j.issn.2224-4778.2014.08.07

Currently, the treatment of advanced colorectal cancer (CRC) differs and oncologists face complicated decisions in the choice of the most suitable treatment options for their patients. Predictive and prognostic biomarkers can simplify clinical decision making. Prognostic factors are those parameters that separate a population in terms of their clinical outcome in the absent of treatment. Predictive factors are those that identifies patients base on clinical outcome in response to particular treatment or lack of response to specific treatment (1,2). Validation of prognostic markers can be performed by data from a retrospective series of patients treated with standard cares. However, analysis of quality randomized clinical trials (RCTs) use for validation of predictive markers (2). Histopathological characteristics such as: the size of the tumor, atypical cell morphology, aberrant expression of protein and recently genetic markers applied to estimate the patient prognosis or predict clinical outcome. In addition, average disease-free survival (DFS), disease-specific survival (DSS), overall survival (OS) or other available statistical data are used for the estimation (3).

Surgical resection is potentially curative for CRC, but Local Recurrences and Distant Metastases progress in 40% of patients (4). At present, the classification of CRC is based on several clinicopathologic factors, including depth of invasive, presence of lymph node metastasis and distant metastasis, which is called tumor node metastases (TNM) staging. Recently, the host lymphoid response to the tumor was included among variables that have shown to be favorable prognostic factors, but translation of knowledge from basic science into daily diagnostic practice is one of the major challenges in routine pathologic reports (5).

From an immunologist's point of view, cytotoxic T lymphocytes (CTLs), classically CD8 T cells can more reliably be considered as a symbol of a systemic anti-tumor immune response (6).

To gain insight use this new variable, several studies were done. These studies show that, the anatomic location of immune cell within the tumor tissue (i.e., intraepithelial, stromal, or advancing border) is very important in this issue and correlates with clinical outcome (7-10). Infiltrating T lymphocytes in direct contact with tumor cells, are often referred to as tumor-infiltrating lymphocytes (TIL), are believed to be directly related to the antitumor immune response. Guidoboni and their colleagues documented that, the presence of CD8 T cells in peri-tumoural and stromal was not correlated with improved prognosis, while the presence of intra-epithelial CD8 T cells was associated with better survival independently of pathological stage (6). Naito *et al.* show that, CD8 T cells infiltrated within cancer cell nets can be a prognostic factor to predict a longer survival of CRC patients (11).

Numerous reports have suggested a correlation between microsatellite instability (MSI), formal Genetic prognostic and predictive marker, and TIL (12-14). According the site of lymphocyte infiltration, TIL can be separated into two types: stromal infiltrating lymphocytes (SIL) and intra-tumor-cell infiltrating lymphocytes (ITCIL). In some previous reports (15-18) the distinction between SIL and ITCIL was not clear. Surely, when dividing TIL into SIL and ITCIL, it is clinically important to determine which type is more closely related to MSI and which is more useful as a survival and recurrence indicator. Takemoto *et al.* showed that SIL consisted of a variety of lymphocytes such as: CD4-, CD8- and S-100-positive cells, while ITCILs

© AME Publishing Company. All rights reserved.

primarily consisted of CD8-positive cells. This study strongly suggests that different factors are involved in the infiltration of SIL and ITCIL, and that intra-tumor cell-infiltration of lymphocytes is caused by MSI (19). A meta-analysis report by Huang *et al*. suggested that, tumor-infiltrating Forkhead box protein P3 (FoxP3) T cells , a transcription factor necessary and sufficient for induction of the immunosuppressive functions of regulatory T cells (Tregs), were a factor for a poor prognosis for HCC and GC, but a good prognosis for CRC (20).

Väyrynen *et al*. show that quantitative evaluation of Crohn's like lymphoid reaction (CLR) density, an inflammatory reaction pattern that consists of numerous transmural lymphoid aggregates, is a relevant prognostic indicator in CRC (21).

In conclusion, data accumulated support the hypothesis that cancer progress is influenced by the host immune system and the presence of immune cells with tumor-suppressive and tumor-promoting activity in the cancer microenvironment and in peripheral blood is usually associated with good clinical outcomes and poor clinical outcomes, respectively (22). New cancer classification using the immunoscore, demonstrating the prevalence of immune infiltrates, has a prognostic significance exceeding that of the TNM classification system. In other words, multivariate Cox analysis have revealed that, the immune criteria remained highly significantly associated with prognosis for all CRC patients (stage I/II/III) (23).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Luo HY, Xu RH. Predictive and prognostic biomarkers with therapeutic targets in advanced colorectal cancer. World J Gastroenterol 2014;20:3858-74.
2. George B, Kopetz S. Predictive and prognostic markers in colorectal cancer. Curr Oncol Rep 2011;13:206-15.
3. Galon J, Pagès F, Marincola FM, et al. The immune score as a new possible approach for the classification of cancer. J Transl Med 2012;10:1.
4. Sandel MH, Dadabayev AR, Menon AG, et al. Prognostic value of tumor-infiltrating dendritic cells in colorectal cancer: role of maturation status and intratumoral localization. Clin Cancer Res 2005;11:2576-82.
5. Belov L, Zhou J, Christopherson RI. Cell surface markers in colorectal cancer prognosis. Int J Mol Sci 2010;12:78-113.
6. Guidoboni M, Gafà R, Viel A, et al. Microsatellite instability and high content of activated cytotoxic lymphocytes identify colon cancer patients with a favorable prognosis. Am J Pathol 2001;159:297-304.
7. Diederichsen AC, Zeuthen J, Christensen PB, et al. Characterisation of tumour infiltrating lymphocytes and correlations with immunological surface molecules in colorectal cancer. Eur J Cancer 1999;35:721-6.
8. Hussein MR. Tumour-infiltrating lymphocytes and melanoma tumorigenesis: an insight. Br J Dermatol 2005;153:18-21.
9. Dunn GP, Dunn IF, Curry WT. Focus on TILs: Prognostic significance of tumor infiltrating lymphocytes in human glioma. Cancer Immun 2007;7:12.
10. Diederichsen AC, Hjelmborg Jv, Christensen PB, et al. Prognostic value of the CD4+/CD8+ ratio of tumour infiltrating lymphocytes in colorectal cancer and HLA-DR expression on tumour cells. Cancer Immunol Immunother 2003;52:423-8.
11. Naito Y, Saito K, Shiiba K, et al. CD8+ T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer. Cancer Res 1998;58:3491-4.
12. Dolcetti R, Viel A, Doglioni C, et al. High prevalence of activated intraepithelial cytotoxic T lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. Am J Pathol 1999;154:1805-13.
13. Jass JR, Do KA, Simms LA, et al. Morphology of sporadic colorectal cancer with DNA replication errors. Gut 1998;42:673-9.
14. Alexander J, Watanabe T, Wu TT, et al. Histopathological identification of colon cancer with microsatellite instability. Am J Pathol 2001;158:527-35.
15. Di Giorgio A, Botti C, Tocchi A, et al. The influence of tumor lymphocytic infiltration on long term survival of surgically treated colorectal cancer patients. Int Surg 1992;77:256-60.
16. Ropponen KM, Eskelinen MJ, Lipponen PK, et al. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.
17. Harrison JC, Dean PJ, el-Zeky F, et al. Impact of the Crohn's-like lymphoid reaction on staging of right-sided colon cancer: results of multivariate analysis. Hum Pathol 1995;26:31-8.
18. Graham DM, Appelman HD. Crohn's-like lymphoid reaction and colorectal carcinoma: a potential histologic prognosticator. Mod Pathol 1990;3:332-5.

© AME Publishing Company. All rights reserved.

19. Takemoto N, Konishi F, Yamashita K, et al. The correlation of microsatellite instability and tumor-infiltrating lymphocytes in hereditary non-polyposis colorectal cancer (HNPCC) and sporadic colorectal cancers: the significance of different types of lymphocyte infiltration. Jpn J Clin Oncol 2004;34:90-8.
20. Huang Y, Liao H, Zhang Y, et al. Prognostic value of tumor-infiltrating FoxP3+ T cells in gastrointestinal cancers: a meta analysis. PLoS One 2014;9:e94376.
21. Väyrynen JP, Sajanti SA, Klintrup K, et al. Characteristics and significance of colorectal cancer associated lymphoid reaction. Int J Cancer 2014;134:2126-35.
22. Gutkin DW, Shurin MR. Clinical evaluation of systemic and local immune responses in cancer: time for integration. Cancer Immunol Immunother 2014;63:45-57.
23. Galon J, Pagès F, Marincola FM, et al. Cancer classification using the Immunoscore: a worldwide task force. J Transl Med 2012;10:205.

Cite this article as: Nazemalhosseini-Mojarad E, Azimzadeh P, Kuppen PJ. Prognostic value of tumor-infiltrating immune cells in patients with colorectal cancer. Transl Gastrointest Cancer 2014;3(4):141-143. doi: 10.3978/j.issn.2224-4778.2014.08.07

© AME Publishing Company. All rights reserved.