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Immune profile of tumor and chemotherapy

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ABSTRACT

Chemotherapy works through its activity on cancer cells. It generally suppresses cell-mediated immunity but also improves cell-mediated immune response by making tumor cells vulnerable to killing by cell-mediated immune responses as well as through its action on immunostimulant and immunosuppressive cells. Outcome of chemotherapy seems to be dependent on baseline tumor-infiltrating immune cells (TII) as well as changes in TII following chemotherapy in varieties of tumors. Evaluation of density and site of two TII is done in immunoscore. It is a better marker than evaluation of a single TII. Evaluation of TII can have prognostic and predictive value and can help in the better stratifying prognostic value of current classification.

Key words: CD4 T cells, CD8 T cells, Cell-mediated immune response, Chemotherapy, Macrophages, Natural killer cells, Predictive biomarker, Prognostic biomarker, T lymphocytes, Treg cells

Introduction

Abnormal proliferation of mutated cells is the key in the initiation of tumor.[1] However, for continued proliferation, evasion of recognition and destruction by the immune system is also required.[1] Immune system is capable of facilitating, preventing or controlling tumor development. Ability of the immune system to facilitate, prevent or control tumor development is known as "cancer immunoediting." Cancer immunoediting is a dynamic process and is composed of three phases - Elimination, Equilibrium, and Escape. Elimination phase is considered responsible for the elimination of proliferation of mutant cells and thereby prevention of detectable tutors. Equilibrium phase is seen in dormant tumors. Escape phases are seen in growing tumors. Escape from immune control is now recognized to be one of the "Hallmarks of Cancer."[1] Type of immunoediting (prevention/control/facilitation) depends on the type, number and site of immune cells infiltrating tumor.[2] Outcome of their interaction is responsible for pathogenesis, prognosis of tumor,[2] as well as response of tumor to therapy. Preclinical studies using immunocompetent and immunodeficient mice demonstrate the importance of immune system for response to chemotherapy. Response to anthracyclines is possible only in the presence of an intact immune system.

Therapeutic interventions (surgery, radiation, chemotherapy, and immunotherapy) are now known to induce changes in type, site, and density of immune cells infiltrating tumor. Pre-existing immune milieu, as well as its alteration by therapeutic intervention, has not only prognostic significance but it also predicts response to therapy.

In this article role played by immune cells in the tumor microenvironment in prognostication and prediction of response to chemotherapy is reviewed.

Immune Cells Infiltrating Human Tumors

All most all type of immune cells are found in the tumor microenvironment and include T lymphocytes, macrophages, natural killer (NK) cells, dendritic cells (DC), myeloid-derived suppressor cells (MDSC), mature B lymphocytes, plasma cells, as well as innate lymphoid cells.[2] They have emerged as powerful immune signatures for various types of human cancer.[3] Of all immune cells infiltrating tumor, tumor-infiltrating lymphocytes (TILs) are extensively studied. CD3+, CD8+, and CD45RO+ T cells are subset of T lymphocytes and are also found to play a major role. Their number, site, and type are found useful to predict the outcome of therapy.[2] Their location and density at the tumor centre and invasive margin combined with the quality of the tertiary lymphoid islets in the affected organ makes the "immunoscore." TILs in isolation or as an immunoscore have been described to be a more powerful prognostic indicator of prognosis than conventional classification system including TNM classification.[2]

Tumor-infiltrating immune cells (TII), CD4+, CD8+, and macrophages are divided into immunostimulant [Th1/Tc1/M1]

and immunosuppressive cells [Th2/Tc2/M2], respectively, based on function and type. Immunostimulant cells generally secrete interleukin (IL)-2 and interferon (IFN) γ and have an antitumor function. Immunosuppressive cells secrete IL-4, IL-5, IL-10, and transforming growth factor (TGF)-β and are protumorigenic. Animal experiments reveal that clinically detectable tumor development is associated with changes in immune balance from Th1/Tc1 to Th2/Tc2. Reversal of this imbalance in cell-mediated immune response (Th2/Tc2 to Th1/Tc1) is associated with response to therapy. Preponderance of immunostimulant cells compared to immunosuppressive cells is associated with a better prognosis.

The development of Th1 responses, alone or linked to the suppression of Th2 responses, has been shown to constitute a positive prognostic marker in cohorts of pancreatic cancer,[4] colorectal cancer (CRC) patients[3] and ovarian carcinoma patients, non-small cell lung cancer (NSCLC), and melanoma.[3] The development of Th2 responses has been associated with poor outcomes in pancreatic cancer patients.[5]

Following section provides an overview of some important immune infiltrating cells:

T lymphocytes

T lymphocytes express an antigen-specific T-cell receptor and CD3. High levels of intratumoral T cells generally constitute a positive prognostic factor. Based on cell surface expression they are either CD8 or CD4. CD8 + T cells (CTLs) and CD4 + T cells (helper T cells) recognize antigens presented on major histocompatibility complex (MHC) Class I or MHC Class II molecules, respectively. Activated T lymphocytes can differentiate into memory T cells, characterized by a CD45RA− CD45RO+ phenotype. Memory T cells induce immune responses against antigens that have already been in contact with the immune system.

CD8+ T cells

Activated cytotoxic T lymphocytes (CTL) are capable of destroying target cells through perforin/granzyme-dependent contact cytolysis. IFN-γ is an effector cytokine secreted by CTLs specifically in peritumoral areas and within tumor nests.

Tumor infiltration by CD8+ T cells has a positive prognostic value in:

1. Breast carcinoma patients[4,6-9]
2. CRC[10]
3. NSCLC[11,12]
4. Ovarian cancer[3]
5. Uroepithelial cancer[3]
6. Rectal cancer[13]
7. Pancreatic cancer[14]
8. Head and neck cancer.[3]

However, high densities of CD8+ T cells in the invasive margins of clear cell renal cell carcinoma (CC RCC)[3] and prostate cancer[3] are associated with poor prognosis (worse progression-free survival [PFS] and overall survival [OS]).

CD8+ CD45RO+ cells

Robust tumor infiltration by CD8+ CD45RO+ cells has been associated with improved disease outcome in:

1. CRC patients[15]
2. NSCLC patients.[16]

Regulatory T cells (Tregs)

Tregs are CD4+ T cells and are characterized by membrane expression of various suppressor molecules (FOXP3+, PD-1, CTLA-4, TIM-3, LAG-3, etc.). They secret various suppressor cytokines and represent another important subset of TIL. Tregs possess potent suppressive function and also exerts suppressive effects on other intratumor immune cells and promote tumor progression.

Density of Treg cells

Their presence generally favors poor prognosis. However, surprisingly their presence is described to correlate with favorable prognosis for patients with bladder cancer,[17] head and neck cancer,[17] and CRC.[17] This is probably due to local protumorigenic inflammation, thereby resulting in opposite outcomes in these two scenarios.

Site of Treg cells

Site of Treg rather than absolute number is also found to have prognostic value in various cancers like ovarian cancer patients.[18]

Ratio of Treg cells and other T lymphocytes

Evaluation of individual cell types with opposite properties (e.g., Treg and CD8 cells) is associated with its own limitations. To overcome this limitations, ratio of both cell types is calculated. The ratio provides more robust information compared to individual cell types. Ratio of Treg/to other T cells within tumor correlates with prognosis in various cancers.[4,19,20] In NSCLC, surgically resected tumors with high ratio experienced worse DSS (median 53 months) when compared with a low ratio. The ratio gets altered in response to therapy also as seen in breast cancer treated with trastuzumab.[21]

Macrophage

Macrophages (literally "big eaters," as from the Greek terms makros "large" and phagein "eat") are tissue-resident myeloid cells. They are responsible for phagocytosis.[17] Macrophages also present antigens to elicit adaptive immune responses.

In solid neoplasms, macrophages comprise a significant portion of tumor tissue. Tumor-associated macrophages (TAM) comprise two distinct types based on cytokines secreted;[17] M1 and M2 macrophage.

M1 macrophage

M1 phenotype accumulates intratumorally and express IFN-γ and IL-2 and tumor necrosis factor (TNF)-α.[22] M1-polarized macrophages recruit Th1 cells to the tumor site.[2] Their preponderance is associated with better outcome in NSCLC.[22] Increased M1/M2 ratio is associated with improved survival in

ovarian cancer.[3] M1 macrophage also improves the sensitivity of lung cancer cell lines to etoposide.[3]

M2 macrophage

M2 phenotype express immunosuppressive cytokines like IL-10.[3] M2 macrophages contribute to tumor growth and progression through local suppression of the immune response at the site of neoplastic transformation (e.g., by the production of high amounts of suppressive cytokine IL-10)[3]. Elevated intratumoral M2 macrophage is associated with poor clinical outcome in breast cancer, NSCLC, melanoma and Hodgkin's lymphoma, and leiomyosarcomas.[8]

MDSC

MDSC represent a heterogeneous population of myeloid cells comprising immature macrophages, granulocytes, and DCs at early stages of differentiation that has pro-tumor effects. They accumulate in the tumor microenvironment, in which they exert their pro-tumor effect by inhibiting innate and adaptive immune response including T-cell proliferation and activation. They are released from the bone marrow in response to cytokines produced by malignant cells and tumor-associated stromal cells. They also promote angiogenesis/lymphangiogenesis, both at the primary tumor site and at distant pre-metastatic niches. Intratumoral MDSCs have a potential to differentiate into TAM. Their presence is associated with disease progression.[3] Accumulation of MDSC within tumor stroma is associated with poor prognosis.[3] Low levels of circulating MDSCs as well as in tumor microenvironment carry a better prognosis.[3] Higher MDSC in peripheral blood, as well as tumor microenvironment, is associated with poor prognosis and response to therapy.[3]

DC

DC being "professional" antigen-presenting cells are often found in tissues of various malignant neoplasms. These cells capture antigens released from apoptotic or necrotic tumor cells and present them to T cells to trigger antitumor immune response and this needs presence of high concentrations of cytokines IFN-γ and TNF. In general, tissue-resident DCs are immature DC (iDC) and are converted to mature DC in the process of antigen presentation. Compared to other antigen presenting cells (including macrophages), mature DCs are most efficient eliciting adaptive immune responses. Tumor tissues usually have increased amounts of IL-10, IL-6, macrophage colony-stimulating factor, etc. This prevents maturation of DCs and leads to accumulation of iDCs.[3] Accumulated iDCs induce T cell energy and immune tolerance toward tumor cells.[3] This contributes to evasion of the tumor from immune surveillance. Thus, elevated tumor infiltrating iDCs carry a poor prognosis and conversely elevated intratumoral mature DCs carry a better prognosis.

NK cells

NK cells are part of the innate immune system. The presence and intensity of NK cell infiltration in tumor stroma may have an impact on the survival of patients with solid tumors like CRC.[23] The magnitude of NK cell antitumor activity significantly depends on the cytokine profile within tumor tissues, and large amounts of NK cells in tumor stroma may not predict their actual antitumor activity.[2]

Tertiary lymphoid structure (TLS)

TLS are cell aggregates[15] structurally resembling lymphoid follicles of the lymph nodes, usually located in the periphery of the tumor at the invasion border. These cell aggregates probably play a central role in the immune infiltration of tumor tissues. TLS development appears to be one of the efficient strategies for immune control of growth and progression of malignant neoplasms.

Chemotherapy-induced Immune Changes

Cytotoxic chemotherapeutic agents are often associated with immunosuppressive side effects including myelosuppression and lymphopenia. However, this provides an opportunity to reset the immune system by Hanahan ande Weinberg[1] favoring the rebound replenishment of various immune cell subsets preferential depletion of immunosuppressive cells emergence of a specific effector cell type with anticancer activity. Decrease in immune suppressive cells such as Tregs and MDSCs is well known following chemotherapy.[5] Chemotherapeutic agents are also known to modulate phenotype of tumor cells by altering the expression of tumor-associated antigens (TAAs), intercellular adhesion molecule 1 (ICAM-1), and other surface molecules making them susceptible to immune-mediated attack.[5]

Moreover, clinical studies demonstrate that chemotherapy often interacts positively with immunotherapy. For instance, CADI-05 and pembrolizumab have been shown to improve the efficacy of platinum doublet in NSCLC and small-cell lung carcinoma.[16,24]

Some of the agents with positive effect are described below:

Monotherapy

Paclitaxel

Paclitaxel can modulate various elements of the host immune system and facilitates the killing of cancer cells by an immune mechanism. Majority of immune modulating activities are seen at non-cytotoxic concentrations of paclitaxel.[25,26]

Paclitaxel decreases immunosuppression by its effect on MDSC and Treg cells. It depletes MDSCs[4] as well as stimulates MDSC differentiation toward DCs.[27] It decreases accumulation and immunosuppressive activities of tumor-infiltrating MDSCs.[27] There is also a significant decrease in the levels of Treg cells. It also prevents polarization of conventional DCs into immunosuppressive regulatory DCs (regDCs)[27] and arrest of the DCs into an immature state.[27]

The decrease in immunosuppressive cells is associated with a strong increase in the amount of effector CD8+ and CD4+

T cells.[27] It increases tumor infiltration by NK cells, CTLs, and macrophages. Paclitaxel induces tumor phenotype with increased permeability to granzyme B[26] to facilitate NK and CTL killing resulting in augmented tumor lysis.[27] Paclitaxel also amplifies antigen-specific Th1 response.[25] Immune modulatory activities of paclitaxel include (i) activation of macrophages and T cells with inhibition of M2 macrophages, (ii) improved antigen presentation,[4] release of inflammatory cytokines in tumors, (iii) increases NK cell and CTL killing by ICAM-1 and mannose-6 receptor expression,[26] and (iv) amplification of antigen-specific Th1 response,[25] and (v) expression of costimulatory molecules.[27]

Docetaxel

Tumors treated *in vivo* with low-dose docetaxel modulate tumor phenotype (increased expression of surface proteins/TAA) and undergo immunogenic modulation with significantly increased sensitivity to antigen-specific cytotoxic T-cell killing.[25] This immunogenic modulation of cancer cells is seen even in cancer cells resistant to docetaxel. It increases IFN-γ by CD8+ cells.[25] Docetaxel depletes MDSCs. Docetaxel administration to patients with breast carcinoma and prostate cancer increases the relative abundance of circulating CTLs over Treg cells and increases the CTL/Treg cell ratio.[4]

Oxaliplatin

Oxaliplatin induces expression of MHC-I proteins and secreted cytokines required for DC maturation and helps antigen processing and T cell activation, resulting in the generation of CTLs with increased cytotoxic potential.[5] It increases the CTL/TREG cell ratio and also depletes MDSCs.[5] It also induces immunogenic cell death in tumor cells.

- Promotes CTL-dependent immune responses.[5]
- Promotes ICD.[5]
- Increases the CTL/TREG cell ratio and depleted MDSCs.[5]

Cisplatin

Cisplatin upregulates ICAM-1, Fas and mannose-6-phosphate receptors on tumor cells for augmented CTL-mediated lysis[26,28] It downregulates PD-L2 expression.[5]

Cyclophosphamide

Cyclophosphamide improves cell-mediated immune response by working on immunosuppressive as well as the immunostimulatory arm of adaptive immunotherapy. Cyclophosphamide abrogates the suppressive influence of Tregs mainly by its depletion.[5,27] It favors expansion of NK cells and Th1 and Th1cells.[5] It augments CTL killing by inducing immunogenic cell death,[5] increasing lytic function as a direct effect and through its effect on the maturation of DC. It also generates the Th1 type of memory T cells.[5] It increases immunosuppression by the expansion of MDSCs.[5]

Doxorubicin

Doxorubicin improves number of immune cells infiltrating tumor and improves immune response.[5] Cancer cells exposed to cytotoxic concentrations of doxorubicin undergo immunogenic cell death, an effect not observed with other DNA-damaging agents.[27] Non-cytotoxic concentrations of doxorubicin enhance IL-12-dependent antigen presentation by DCs, leading to increased effector T cell function.[26]

It induces a significant influx of CD8+ T cells into the tumor bed and also enhances its cytotoxic effect of CD8+ T cells.[25] Doxorubicin upregulates mannose-6-phosphate receptors on tumor cells and increases their permeability to granzyme B to facilitate NK and CTL killing.[26] It increases the expression of NKG2D ligands on tumor cells to facilitate killing by NK cells. It decreases the density of immunosuppressive cells: Treg cells and monocytic MDSCs.[3]

Gemcitabine

Gemcitabine depletes the amount of circulating MDSCs and Treg[5,27] favors the reprogramming of TAMs toward an immunostimulatory phenotype. Besides such direct immunostimulatory effects, gemcitabine stimulates the expression of MHC Class I molecules and NKG2D ligands by cancer cells,[5] and thereby increasing their antigenicity.

Pemetrexed

Pemetrexed activates IFN-γ producing NK cells but depletes CD45RO+ memory T cells.[5]

Vinblastine

Vinblastine induces the phenotypic and functional maturation of DCs by increasing expression of the costimulatory molecules CD40, CD80, and CD86, as well as MHCII, IL-1, and IL-6, significantly augmenting their capacity to stimulate T cells.[27]

Imatinib

Imatinib reduces tumor-induced immunosuppression by its effect on Treg and Indolamine 2,3-dioxygenase (IDO).[25] It interferes with immunosuppressive functions of Treg cells.[25] It also limits IDO expression by tumor cells. It has a positive effect on TNF-secreting CD4+ T cells and NK cell.[5] It promotes tumor-infiltrating CTLs and NK cells.[5] However, it inhibits antigen-specific memory CD8+ T cells *in vivo*[25] and favors the relative accumulation of M2 TAMs.[5] Overall, there is an increase in effector function.

Sunitinib

Sunitinib mainly decreases immunosuppression by limiting infiltration by Treg cells and MDSCs while inhibiting STAT3 activity.[25] It increases infiltration of CTLs and increases the ratio of CTL:Treg.[4]

5-Fluorouracil (FU)

5-FU increases CTL-mediated immune response[5] by increasing frequency of tumor-infiltrating CTLs[5] and also enhances the sensitivity of tumor cells to the cytotoxic effects of CD8+ T cells by inducing expression of MHC Class I, ICAM-1, and Fas.[5] 5-FU favors MDSC differentiation[5] and also depletes MDSCs in preclinical models.[5,27]

Fludarabine
Fludarabine is a potent inhibitor of Treg.[5] It also generates memory T cells.[5]

Azacytidine
Azacytidine enhances tumor antigenicity by upregulating MHC Class I and tumor antigen expression, increasing the release of pro-inflammatory cytokines and danger signals, and promoting antigen uptake by DC and killing by NK cells.[25] It also increases the expression of costimulatory molecules[27] and also increases the ability of human DCs to stimulate the proliferation of allogeneic T lymphocytes.[27]

Bevacizumab
It depletes circulating Treg cells and replete B and T cell compartments.[25] It favors the differentiation of DCs and facilitates tumor infiltration by lymphocytes.[25]

Trastuzumab
Trastuzumab favors the generation of human epidermal growth factor receptor 2 (HER2)-specific CD8+ cells,[25] CD4 cells and stimulates tumor infiltration by NK cells.[25] It decreases Treg cells[21] and decreases the ratio of Treg/Th17 cells.[21]

Dasatinib
It favors the expansion of circulating CTLs and NK cells[5] and depletes tumor-infiltrating Treg cells and MDSCs.[5]

Decitabine
It triggers a Type I IFN response[5] and upregulates antigen presentation.[5] It depletes MDSCs.[5]

Erlotinib-Gefitinib
They upregulate NKG2D ligands and MHC Class I on cancer cells and help in innate as well as adaptive immune response.[5]

Carboplatin
It downregulates PD-L2.[5]

Combination therapy

In cancer management, chemotherapy is used as combination therapy in majority cancers. The components of particularly efficient chemotherapeutic regimens appear to cooperate not only for their cytotoxic effects due to different modes of action but also by exerting multipronged immunostimulatory effects.

5-FU+ Irinotecan[5]
The effect of 5-FU on depletion of MDSC is lost when 5-FU is combined with irinotecan, which blocks MDSC death and supports the expansion of circulating MDSCs.[5] This may explain the superiority of FOLFOX regimen (folinic acid, 5-FU, and oxaliplatin) compared to FOLFIRI regimen (folinic acid, 5-FU, and irinotecan) in the treatment of CRC.

5-FU+ oxaliplatin
They retain activity of 5-FU to depletes circulating MDSCs.[5]

Gemcitabine + cisplatin
They deplete circulating Treg cells.[5]

Vinorelbine + cisplatin
a. Transiently modulates Treg function and induces a sharp and sustained decline in Treg numbers.[28]
b. Induces sub-myeloablative leucopenia that differentially modulates reconstitution of Treg versus CTL resulting in a relative increase in CTL.[28] (1.5- and 2-fold increase in CD4+/Treg ratio 4 and 7 days post-chemotherapy, respectively).
c. Modulates expression of survival genes and tumor cell phenotype and increases sensitivity to CTL-mediated killing.[28]
d. Markedly decreases the protein secretion ratio of TGF-b/IL-8 and has synergy with the vaccine, resulting in enhancement of antigen-specific CD4+ and CD8+ immune response.[28]
e. Increases the CTL/TREG cell ratio.[5]

Immune Profiling of Tumor Infiltrate and Immunoscore

In surgically resected tumors, CD3+ T cells, CD8+ T cells, and CD45RO+ CD8+ memory effector T cells are found to be correlated with prognosis.[20] High densities of CD8+ T cells generally correlates with favorable prognosis irrespective of its location within tumor or at margin.[14,29]

Efforts to improve the prognostic and predictive value of T lymphocyte have led to development immunoscore[29] following an extensive evaluation of early CRCs treated surgically. Immunoscore is based on densities of any two of three T lymphocyte (CD3+, CD8+, or CD45+ cells) within the center of tumor and invasive margins.[29] It ranges from 0 to 4 with 4 assigned to tumors having high densities of both cells populations in both regions.[29] In early CRC, densities of CD45RO+ and CD8+ cells in tumor regions (Center of Tumor/Invasive Margin) classified the patients into four distinct prognostic groups with significant differences in disease-free, disease-specific, and OS (all $P < 0.0001$).[30] 5 years after diagnosis, patients with high densities of CD8+ and CD45RO+ cells had lower recurrence rate (4.8%; 95% confidence interval (CI), 0.6–8.8 vs. 75%; 95% CI, 17%–92.5%; $P < 0.0001$) and improved survival (86.2%; 95% CI 79.4%–93.6% vs. 27.5%; 95% CI, 10.5%–72%; $P < 0.0001$) compared to patients with low density of CD8+ and CD45RO+ cells.[30] Immunoscore has also been evaluated in NSCLC.[31] Immunoscore also had independent effects on the rates of complete remission.[30] Immunoscore is found to provide better prognostication compared to TNM classification and can be viewed as a subset of each TNM stage for better prognostication of PFS and OS.[30] Immunoscore though useful in early cancers amenable to surgery needs evaluation for advanced cancers not amenable to surgery.

The following section provides an overview of prognostic and predictive values of various infiltrating immune cells.

Tumor immune infiltrates as a prognostic biomarker for response to chemotherapy

The outcome of chemotherapy is variable and different, in spite of identical phenotype and histological features. This can be explained, at least in part, by density, type, and site of TII. From studies done so far, it emerges that prognosis of therapy can be better predicted by residual immune activation present in a tumor at the time of diagnosis. Th1 type of cell-mediated immune response is strongly associated with improved survival in many human cancers[27] including pancreatic cancer,[5] CRC patients, ovarian carcinoma patients, NSCLC, melanoma.[3] The development of Th2 responses has been associated with poor outcomes in pancreatic cancer patients.[5]

In general, infiltration by CD8+ T cells is associated with better prognosis and Treg is associated with poor prognosis.[27] Majority of outcome studies are based on neoadjuvant or adjuvant settings as it provides an adequate amount of tissues.

The following section provides an overview of immune infiltrates as a prognostic biomarker in various cancers.

Breast cancer

In triple negative and HER2 +ve breast cancer, higher TII is associated with better outcome.[5,7] In patients with triple-negative breast cancer (TNBC), every 10% increase in stromal TILs is associated with a 14% reduction of risk of recurrence or death (Ptx = 0.02), and 18% reduction of risk of distant recurrence (P = 0.04) and 19% reduction of risk of death (P = 0.01) were observed.[7]

1. TIIs (low, intermediate, and high) proved to have significant prognostic value (P = 0.015) regarding relapse-free survival (RFS) in TNBC (P = 0.097) but not among HER2+ve breast cancer treated with chemotherapy. The prognosis was also significantly poor in TNBC patients in the low-TII group compared with the intermediate/high-TII groups (hazard ratio [HR]: 2.49; 95% CI: 1.05–5.55).[32]

Colorectal carcinoma

Besides Th1 type of immune response, a number of tumor-infiltrating CD8+ T cells are associated with a better prognosis[30] for better prognostication. Compared to individual cells, immunoscore has better prognostic value. Highest immunoscore (higher CD8 and CD45RO cells) is associated with lower tumor recurrence (4.8%) and better survival 86.2% at 5 years compared to lowest immunoscore which is associated with higher tumor recurrence(75%) and 27.5% survival at 5 years.[30]

NK cell infiltration also has prognostic value. Higher infiltrating NK cell has better 5 years survival compared to tumors with lower infiltrating NK cells in spite of same TNM staging of disease.[23]

Tumor-infiltrating high FOXP3:CD4 (P = 0.03) and FOXP3:CD8 (P = 0.05) ratios are associated with shorter OS.[19]

Non-small cell lung cancer

Higher CD8+ and M1 macrophage indicate favorable prognosis and Treg with poor survival.[3,22] Similarly, density of mature DC is an independent prognostic factor.[3] Higher ratio of FOXP3+ to CD3 also has a higher risk of relapse.

M1 macrophage infiltrates also has prognostic value with 5 years survival >75% for patients with higher than median values and <5% for lower values.[22]

Ovarian cancer

Infiltration of tumor with CD4+ T cells is associated with better prognosis in non-serous ovarian cancer and CD8+ cells in advanced CC carcinoma.[5] A high ratio of CD8+ over FOXP3+ TIIs is also a positive prognostic factor for OS.[20]

Higher M1/M2 ratios of TAM are also a better prognostic parameter.[3]

CC RCC

Infiltration with CD8+ T cells in primary and metastatic sites in CC carcinoma is associated with poor PFS and OS.[3] This may be due to PD-1 expression and coincident PD-L1 expression on tumor. CC RCC also expresses PD-1 and LAG-3 and suggests a poor outcome.

Uroepithelial carcinoma

A high frequency of CD8+ TII is a positive prognostic factor for OS.[3]

Hepatocellular carcinoma

Infiltration by Th1 cells and CD8+CD45RO+ T cells has a positive prognostic impact while Treg has a negative impact on OS.[3]

Oropharyngeal cancer

In HPV positive oropharyngeal cancers, higher TII is associated with better prognosis (HR 0.28; 95% CI 0.13–0.62; P = 0.002).[33]

Melanoma

TIIs have a positive prognostic value on OS in primary cutaneous melanoma[3] with reduced potential for metastasis.[7] TII also prognosticate DFS in adjuvant and neoadjuvant setting.[5]

TII as predictive biomarkers for efficacy of chemotherapy

Besides prognostication, TII is also found useful in predicting response to chemotherapy as well as resistance to chemotherapy. Chemotherapeutic agents vary in their effects on immune cells as described in the previous section. Predictive value of TII depends their baseline value (type, density, and location) as well as changes brought about by therapy. Majority of such observations are made through studies in

neoadjuvant and adjuvant settings as it provides adequate opportunities for evaluation. This should be considered as a trend for advanced metastatic cancer as they have significantly higher immunosuppression. The following section provides an overview of immune infiltrates as predictive biomarkers for the efficacy of chemotherapy in various cancers.

Breast cancer

Baseline predictor of better prognosis

Following immune parameters at pre-treatment biopsy predict better outcome:

1. MHC Class-I staining of tumor cells and FOXP3+ staining of T cell infiltrates predict improved PFS with systemic cyclophosphamide-based chemotherapy ($P = 0.013$).[34]
2. HER-2 +ve breast cancer:
   a. In a triple negative HER-2 positive breast cancer, each 10% increase in TIIs predicts increased distant DFS with HR 0.77 (95% CI, 0.61–0.98; $P = 0.02$).[7]
3. TII count predicts pathological complete response (PCR) (odds ratio [OR], 4.77; 95% CI, 1.05–21.6; $P = 0.043$).[35]
4. High CD8+ TII predicts the better outcome with anthracycline-based therapy. (HR 0.36; 95% CI, 0.15 to 0.84; $P = 0.0177$), in HER2+ve and triple-negative tumor phenotypes. TII predicts response to anthracycline-based chemotherapy in ER−ve breast cancer.[6]
5. High levels of intraepithelial CD3+ TII predicts increased DFS for adjuvant anthracycline-based therapy ($P = 0.0023$).[6]

Baseline predictor of poor prognosis

Tumor infiltration by T cells has a favorable prognostic impact in HER2+ve and estrogen receptor (ER)−ve cancers and TNBC.[3,7] Loss of function mutations in TLR4 predicts early relapse following anthracycline-based chemotherapy.[25]

Baseline predictor of PCR in breast cancer following neoadjuvant therapy

Following baseline immune parameters predict PCR.

1. High levels of CD3+ or CD83+ cells (mature DC).[3]
2. Presence of CD8+ and CD4+ cells predicts complete pathogenic response to neoadjuvant therapy.[35]
3. In the patients receiving trastuzumab, high TII predicts higher pCR rate (OR, 2.06; 95% CI, 1.21–3.5; $P = 0.008$).[36]
4. The predictive value of high CD8+ TIIs for pCR was significant (OR, 34.84; 95% CI, 9.48–127.96, $P < 0.001$) in a meta-analysis of 13100 cases.[4]
5. TIIs >5% predict higher PCR rates independent of treatment group (OR, 2.60; 95% CI, 1.26–5.39).[4]
6. Higher CD8+/CD4+ ratio predicts PCR. ($P = 0.018$). CD8+ TIIs (OR, 9.786; 95% CI, 2.121–45.149; $P = 0.003$) were independent predictive factors for PCR.[8]
7. Higher CD8+ TIIs predicts PCR group for anthracycline-containing therapy.[8]
8. In patients with ER-ve tumors treated with neoadjuvant anthracycline-based chemotherapy, TII predicts PCR (74% TII-high patients vs. 31% TII-low patients OR, 6.33; 95%CI, 2.49 to 16.08; $P < 0.0001$).[6] Furthermore, identical PCR rates are seen in TNBC.
9. TII is an independent parameter for PCR (OR 6.42; 95% CI, 2.08 to 19.8; $P = 0.001$), from standard pathologic parameters.[6]
10. TNBCs with the high CD8+ TII group for residual tumors compared to low CD8+ TII group had significantly better RFS (73% vs 30%; $P < 0.0001$) and HR, 3.09; (95% CI, 1.537–6.614; $P = 0.0013$) and breast cancer-specific survival (BCCS) (86% vs. 42%; $P < 0.0001$).[9]
11. TNBCs with a higher CD8/FOXP3 ratio compared with a lower CD8/FOXP3 ratio were also significantly correlated with better 5 years RFS (72% vs. 40%; $P = 0.009$) with HR 2.07; 95% CI 1.029–4.436; $P = 0.0412$ and BCSS (77% vs. 56% $P = 0.027$).[9]
12. High CD8+ TII levels and CD8/FOXP3 ratio in residual tumors could accurately predict the better clinical outcome in TNBC patients with non-PCR following neoadjuvant chemotherapy (NAC) (RFS [73% vs. 30%; $P < 0.0001$] with HR 3.09; 95% CI, 1.537–6.614; $P = 0.0013$ and BCSS [86% vs. 42%; $P < 0.0001$]).[9]
13. Group having PCR and high TII has a better prognosis and subgroup with no PCR, and low TII has a worse prognosis ($P = 0.039$).[36]
14. TIIs were significantly related to PCR ratio in TNBC ($P = 0.024$).[32]

Changes immune biomarker following chemotherapy and response prediction

1. Increased TII following chemotherapy predicts PCR to NAC and improved time to tumor recurrence (TTR) and OS to adjuvant therapy.[3]
2. Increased CTL/Treg ratio predicts PCR to neoadjuvant anthracycline-based therapy. It predicts PCR even when such changes are seen after one cycle of anthracycline-based chemotherapy.[3,5]
3. Increased CTL/Treg ratio predicts improved RFS and OS to neoadjuvant based paclitaxel therapy and TTR and OS adjuvant therapy.[3]
4. High intratumoral levels of CD8+ CTLs at surgery following neoadjuvant paclitaxel-based chemotherapy, correlate with improved RFS and OS.[5]
5. Increased TAM predicts shorter RFS and OS.[5]
6. High CD8 and low FOXP3 cell infiltrate after chemotherapy predicts improved RFS ($P = 0.02$) and OS ($P = 0.002$) as an independent predictor. A combined score associating CD8/FOXP3 ratio and pathological American Joint Committee on Cancer staging identifies a subgroup of patients with a significantly better long-term OS (100%).
7. TNBCs with a higher increase in CD8+ TII group had a significantly better RFS than those with a lower increase ($P = 0.011$), with the 5 years RFS rates 74% and 20%, respectively.[9]
8. TNBCs with a higher increase in CD8/FOXP3 ratio compared to low rate of changes in CD8/FOXP3 had

a lower recurrence rate (25% vs. 61%; $P = 0.0352$),[14] significantly better 5-year RFS (68% vs 41%; $P = 0.011$) and BCSS (78% vs. 58%; $P = 0.023$).[9]

HER-2+ve breast cancers

1. Trastuzumab therapy results in a decrease in Treg and increase in Th17 cells.[21]
2. This leads to decreased ratio of circulating Treg/Th17 cells after trastuzumab therapy and improved outcome.[21] The changes in cell-mediated immune response are sustained following therapy also.

CRC

TII predicts survival benefit in CRC treated with 5-FU-based chemotherapy.[3] Infiltration of tumor with CD56+ve cells (NK cells) predicts response to cetuximab as well as improved PFS.[23]

In a metastatic CRC, TII in tumor, as well as metastatic lesion, is a better predictor for survival in synchronous metastasis compared to metachronous metastases (HR 3.696; 95% CI 1.935–7.060; $P = <0.001$).[10]

CRC with liver metastasis

TII densities at the invasive margin of liver metastasis predict response to chemotherapy with a sensitivity of 79% and specificity of 100%.[37] CD3, CD8, or Granzyme B positive immune cells at the invasive margins of liver metastasis also predict treatment response[10,30] and prolongs RFS. Higher TII is also associated with improved RFS ($P = 0.001$) and OS ($P = 0.0018$).[37]

Increased TII following chemotherapy also suggest improved OS.[6]

NSCLC

In adjuvant setting, in Stage II and III settings, higher CD8+ TII predicts low recurrence rate ($P = 0.018$) and highest immunoscore predicts better DFS.[31] Similarly, in Stage-I disease also is high CD8+TIIs predicts better DFS (HR 0.393; 95% CI 0.217–0.714; $P = 0.002$) and OS (HR 0.505; 95% CI, 0.259–0.982; $P = 0.044$).[11] In another study involving adenocarcinoma of lung, high CD8+ TII in adjuvant settings were associated with better DFS (HR 0.41; 95% CI, 0.21–0.82; $P = 0.012$).[12]

CD8+ TIIs are effective prognostic predictors. High CD8+TIIs are significantly associated with better DFS (HR 0.393; 95% CI, 0.217–0.714; $P = 0.002$). Only CD8+TIIs expression is associated with OS (HR 0.505; 95% CI, 0.259–0.982; $P = 0.044$).

Ovarian cancer

The presence of intratumoral CD3+ T cells independently predicts delayed recurrence or delayed death following:

i. Platinum-based chemotherapy in advanced ovarian cancer with 5-year OS rate of 38.0% among patients whose tumors contained T cells and 4.5% among patients whose tumors contained no T cells.[20]
ii. Complete clinical response after debulking and platinum-based chemotherapy with 5-year survival rate was 73.9% among patients whose tumors contained T cells and 11.9% among patients whose tumors contained no T cells.[20]

Higher CD3+ and CD8+ T cells within the stroma also predict response to platinum-based chemotherapy with improved survival following adjuvant chemotherapy in patients with higher CD8+ T cells.[4,5]

CD27 subset of CD8+ T cell infiltration is associated with better DFS in adjuvant setting (HR 0.23; 95% CI 0.10–0.56; $P = 0.001$).[27] In neoadjuvant setting, TII has no prognostic value.[27]

In the adjuvant setting, use of platinum-based chemotherapy is associated 5-year OS rate of 73.9% in patients having T cell infiltration compared to 11.9% for patients with absence of T cell infiltration ($P < 0.001$).[28]

Gastrointestinal stromal tumors

Higher TII predicts improved PFS to imatinib-based therapy.[5] Increased production of IFN-γ by circulating NK cells after imatinib treatment predicts prolonged time to progression.

Biliary tract cancer

High TII is associated with improved OS to adjuvant therapy.[5] Therapy can be multimodal.[5]

Rectal cancer

The density of CD4+, as well as CD8+ T cells, was highly correlated with tumor response as well as with the rate of decrease in tumor size following NAC ($P = 0.0013$, 0.0020).[13] Immunoscore was originally designed based on studies involving patients with CRC undergoing surgical treatment is also useful in rectal cancer[5] and provides better prognostication.

Pancreatic cancer

Increased Th2/Th1 ratio predicts shortened OS following adjuvant therapy.[5] High TAM predicts response to gemcitabine-based therapy.[5] Higher CD8+ TII is a predictor of better OS (HR 0.474; 95% CI 0.251–0.893; $P = 0.021$) and PFS (HR 0.556; 95% CI 0.313–0.988; $P = 0.045$).[14]

Esophageal adenocarcinoma

Higher levels of TIIs in the pathological specimen were associated with significant pathological response to NAC. On multivariate analysis increased levels of CD4+ ($P = 0.017$) and CD8+ TIIs ($P = 0.005$) were associated with significant local tumor regression and lymph node downstaging, respectively.[38]

Oropharyngeal cancer

Higher baseline CD3+ cells predict better OS following cisplatin-based chemotherapy (HR, 0.39; 95% CI 0.21–0.73; $P = 0.003$).[39]

Head and neck cancer

High expression of CD3 TII predicts significantly better OS (HR 0.429; 95% CI 0.206–0.895; $P = 0.024$) and PFS (HR

0.494; 95% CI 0.248–0.982; $P = 0.044$) following definitive chemoradiotherapy. Similarly, high CD8+ TII also predicts better OS (HR 0.359; 95% CI 0.130–0.990; $P = 0.028$) and PFS (HR, 0.464; 95% CI 0.198–1.087; $P = 0.047$).[40]

Melanoma

Melanoma is considered an immunological tumor. Higher circulating CD4 cells and low T reg cells predict response to neoadjuvant dacarbazine.[5] High infiltrating CTL predicts improved OS to adjuvant therapy.[5] Tumors with high levels of CD3+ and CD8+ cells around metastases predict improved OS following neoadjuvant and/or adjuvant chemotherapy.[5]

Conclusion

TIIs seem to play an important role in response to chemotherapy. Evaluation of TII in combination with conventional classification may improve the prognostic and predictive value of classification.

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