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Chapter

Immuno-Oncology, Imaging Biomarkers and Response to Chemotherapy in Cancer Treatment

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Abstract

Immuno-oncology is a young and growing field in cancer therapy. It stimulates immune system to target and attack the tumor or inhibiting the immune response. Recent findings in cancer immunotherapy has revealed that the immune system can control many cancers across various histologies, producing durable responses in a way which not seen with many small molecule drugs. Advances in understanding the role and molecular mechanisms of immunotherapy are revolutionizing clinical practice in cancer treatment. Immunotherapy is being intensively explored with the aim of improving primary response rates or prolonging overall survival. The purpose of this chapter is to review the different aspect of immunotherapy including blockade of immunological checkpoints, immuno-oncology and imaging biomarkers, immune response, therapeutic resistance and combination therapy, while several additional immuno-therapeutic strategies are also highlighted.

Keywords: immune response, immunotherapy, immuno-oncology, cancer

1. Introduction

Cancer plays a serious role in public health bother. Global demographic features increase the predicted incidence of cancer in the coming decades. Annually, cancer is expected to reach 420 million new cases by 2025. Female breast cancer, colorectal, prostate, and lung are often diagnostic cancers in Europe, while lung cancer is the leading explanation for cancer and death worldwide [1]. The increasing information of biology and tumors over the past 15 years has considerably modified the pattern of cancer. Throughout the past decades, immune therapy has been used as a promising approach to the treatment of a broad variety of human cancers. But these methods such as chemotherapy and radiotherapy seem to be effective enough due to the problems including low target property, drug resistance, severe side effects and immuno-therapies induce host immune system to promote a response against tumors [2]. An important feature of Immunotherapy is to kill malignant tumors whereas healthy tissues not damaged. The issue of immunotherapy is to expand strategies that effectively and securely enhance anti-tumor responses. A few current cancer immunotherapy methods tested for their effectiveness include cytokine

treatment, cell-receptor cell transfer, cancer vaccines and monoclonal antibodies (mAbs). The most encouraging of these approaches are those that are specific T-cell stimulants that are capable of long-term tumor immunity [3]. The activity and regulation of T-cell is vital for the development of the tumor, since T-cells have the ability to remove cancerous cells [4].

2. Checkpoint blockade in immuno-oncology therapy

Checkpoint inhibitors are immune synapses which decrease the function of T-lymphocyte [5]. They are against autoimmunity and systemic inflammations. These mechanisms help tumor to escape from immune detection [2, 5]. The most frequent useful checkpoint inhibitor is checkpoint inhibitor mAbs, anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) [6, 7]. Checkpoint inhibitors invigorate immune system and persuade tumors. However, stimulation of cancerous T-cell proliferation can provide non-Hodgkin lymphoma (NHL) [2, 8]. Complication of checkpoint inhibitors is an autoimmune disease. Due to PD-1 or CTLA-4 illustrates beneficial result on advanced-stage melanoma [2, 9]. So, cytotoxic T lymphocyte antigen-4 and B7.1 are the most frequent targets in Immunotherapy. They can manage the interaction between T-cell and dendritic cells [1, 10].

2.1 PD-1

PD-1 is a receptor which is increased by T-cells during peripheral activation. PD-1 blockade down regulates the activity of intramural T regulatory cells [10]. Tumors can evade from immune system by inhibiting PD-1. Also, PD-1 is expressed by other immune cells such as lymphocyte B, natural killer (NK) cells and dendritic cells [4, 11–13]. PD-L1 has two ligands including PD-L1 (B7-H1) and PD-L2 (B7-H2). These two ligands expressed by inflammation and tumors tissues [4, 14]. Also, these ligands are expressed on antigen presenting cell (APCs). In addition, tumor tissues express these ligands [13]. PD-1 reduces the activity of T-cells later than CTLA-4. So, PD-1 influences on immune response during the chronic inflammation. PD-1 is important for the monitoring of Tregs suppressor performance [4]. CD80 or B7-1 is linked to PD-L1. Bidirectional interactions can inhibit PD-L1 and B7-1. Evading of PD-1 from immune diagnosis is so important [13]. Overall, PD-L1 in cancer is related to poor prognosis and larger tumor size and reduction in cytotoxic activity [4, 15, 16]. But, PD-1 can stop NHL by diminishing the proliferation of cancerous T-cells [15]. PD-L2 only can regulate the responses of Th2. But, PD-L2 is not selected as a target in cancer. PD-L2 does not have strong relation with survival. However, PD-L1 has the most potent influence and anti-tumor Th1 responses [4, 9]. PD-L1 is a useful ligand to manage several cancers like melanoma, non-small cell lung cancer (NSCLC) and kidney cancer [9].

2.2 CTLA-4

Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a glycoprotein that exists on the surface of T cells [1]. When T-cells activation is regulated in its early stage, T-cells in central lymph nodes express CTLA-4. CTLA-4 which is expressed by regulatory T cells (Tregs) can control the activated lymphocyte's proliferation in the lymph nodes. CTLA-4 plays a role in joining to B7·1 and B7·2 and involves with CD28. So, CTLA-4 can discontinue the activation and production of T cells. Anti-CTLA-4 decreases the Tregs cell to promote the proliferation of T cells [2, 10].

2.3 CD73

The investigations on anti-CD73 or anti-adenosine phase 1 found that they could effectively provoke immune response and improve the functions of first generation immune checkpoint inhibitors [17]. CD73 in Triple-negative breast cancer have poor prognosis [18]. Estrogen receptor (ER) negative has poor prognosis as well. CD73 in ER positive has no prognostic value. Stages I–III have good prognosis [19]. CD73 in B-cell acute lymphoblastic leukemia is a marker of minimal residual disease. B-cell chronic lymphocytic leukemia expresses CD73 as a marker of aggressiveness. CD73 is associated with CD38 and ZAP70 expression; two markers of disease progression in B-cell chronic lymphocytic leukemia [18, 20, 21]. CD73 in glioblastoma multiform (GBM) has poor prognosis [17]. CD73 is associated with limited metastatic potential in melanoma [17]. High-grade serous CD73 expression shows poor prognosis in ovarian cancers. However, CD73 expression indicated good prognosis in Epithelial ovarian cancer [17].

3. First group of immunotherapy medication

3.1 Ipilimumab (Yervoy)

Ipilimumab is a fully human immunoglobulin G1 (IgG1) monoclonal. It up regulates T-cell activation by targeting CTLA-4 and is used in phase 2 data for tumor response and safety by logistic regression models. Ipilimumab dosage is about 0.3, 3, and 10 mg/kg every 3 weeks for maximum four doses. About 10 mg/kg doses of Ipilimumab are more effective than 3 mg/kg in metastatic melanoma. However, 10 mg/kg doses of Ipilimumab have more serious side effects [1, 22, 23]. Clinical efficacy of Ipilimumab shows strong improvement on survival. Its response rate is 9–18% in phase III clinical trial in patients with NSCLC. Also, treatment scenario for Ipilimumab is pretreated and its control arm is Docetaxel. Response rate in patient with melanoma in phase 3 trial is p100 10.9 mo vs. 1.5 mo. Treatment scenario for Ipilimumab is pretreated in management of melanoma [1].

3.2 Tremelimumab

Tremelimumab is fully humanized IgG2 antibody and its target cell is T lymphocyte. Tremelimumab affects T lymphocyte by targeting CTL-4 and is an immune checkpoint inhibitor in hepatocellular carcinoma (HCC) clinical trials [1]. The effect of Tremelimumab has recently been studied in combination with Durvalumab on HCC. The response rate of this combination on HCC was approximately 25%. In phase 3 on metastatic melanoma, Tremelimumab can increase overall survival in comparison to chemotherapy [10]. It is given every 3 weeks for the management of melanoma and has 10% response rate [1]. Another study on phase 1 clinical trial has shown that the combination of Tremelimumab and CP-893,870 (a CD40-agonist mAb) provides the 27% objective response rate and 26 months overall survival. Also this combination provides 8% complete response rate [2].

3.3 Pembrolizumab (Keytruda)

Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1. It has only influence on tumors express programmed death-ligand 1 (PD-L1) [4, 24]. Pembrolizumab is recommended for the management of advance melanoma along with Ipilimumab. The recommended dosage is 2 mg/kg each 3 weeks in phase 1

clinical trial in patient with metastatic melanoma [1, 4, 24]. Also, Pembrolizumab is suggested for the treatment of metastatic NSCLC [4]. This drug has been studied in various cancer including gastric/gastroesophageal junction cancer (phase III), NSCLC (phase III), squamous cell carcinoma of the head and neck (SCCHN) (phase III), urothelial cancer (phase III), colorectal carcinoma (phase II), gastric/gastroesophageal junction cancer (phase II), GBM Merkel cell carcinoma (phase II), Hodgkin lymphoma (HL) and NHL (phase II). Pembrolizumab is one of the most important immune checkpoint inhibitors in HCC clinical trials. Response rate of Pembrolizumab is about 25 vs. 4% in patients with melanoma in phase II clinical trial. Also its control arm is investigator's choice chemotherapy. Also, using Pembrolizumab, as first line in treatment of melanoma, has 33.7 vs. 11.9% response rate in phase 3 clinical trial [23]. A recent study shows the saturations of Pemberolizumab is reached to 95% by dosage of 1 mg/kg every 3 week. Some studies revealed that reaching to complete achievement of the goal is 64% by 1 mg/kg each 3 week. However, complete achievements ≥2 mg/kg (such as 10 mg/kg) is higher 90% [25]. Later study has found that Pembrolizumab illustrates equivalence in exposure at dosage body weight-based 2-mg/kg each 3 week. But, Nivolumab does not have equality in exposure at indefinite quantity of two hundred mg each 3 weeks [24, 26]. Pembrolizumab clearance decreases about 20% after first injection. But this clearance is not clinically important [24, 27]. Common side effects of Pembrolizumab are fatigue, pruritus, and decreased appetite. Recent study in lung cancer patients shows 50% of tumors cell has PD-L1 receptors. In addition, Pembrolizumab has 45.2% response rate in patients who has PD-L1 receptors. But, objective response rate is 19.4% through all patients with metastatic lung cancer [27].

3.4 Blinatumomab (connecting bi-specific antibodies)

Blinatumomab is approved for CD19+ B-cell malignancies and its pre-clinical finding has strong in-vitro cytolytic activity. Blinatumomab's pharmacokinetics has clear kinetics and can trigger T lymphocytes to reach tumors cell. One of the recent studies on Blinatumomab shows that its clinical efficacy has high response rates, and its safety has moderate to severe toxicity [23].

3.5 Nivolumab (Optivo)

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that targets PD-1. Nivolumab target cell is T lymphocyte and is accepted in cancer with expressing PD-L1 and also without expressing PD-L1 [4]. Nivolumab dosage is about 1–10 mg/kg. Also non-clinical data recommends 0.3 mg/kg as initial dose. Low-immunogenic tumor types needed higher Nivolumab dosage. For instance, beneficial dosage for melanoma and renal cell carcinoma (immunogenic tumors) is 1–10 mg/kg (1 mg/kg each 2 week) [26]. However, higher dosage (3 and 10 mg/kg each 2 week) needs for NSCLC. Thus, lower dose level can have longer progression-free survival in immunogenic tumor types. Nivolumab is approved for both PD-L1 expressers [24, 28]. Recent studies indicate that Nivolumab has increased the survival in patients with melanoma [28, 29]. Nivolumab has 25–40% response rate with long lasting response (2 years) in patients with melanoma. Another study in phase III trial has shown Nivolumab has increased survival in comparison with chemotherapy in patients with advance melanoma and advance NSCLC [4]. Nivolumab should be selected 3 mg/kg each 2 week as monotherapy dose for different type of tumors to improve survival [30]. The investigation exhibited that there was a linear relationship between Nivolumab pharmacokinetics and the dose range. For renal cell carcinoma, metastatic melanoma and NSCLC, suggested dosage is

240 mg IV every 2 week depends on population pharmacokinetics analyses and response analyses of dose and exposure [31]. Also, Nivolumab is prescribed for renal cell carcinoma due to second choice. Pharmacometrics has main role in changing body weight based on dosage to flat dosage. The advantages of using a flat dose include removing excess material waste, the convenience of health care providers, and reducing worries about the exact dose in patients with weight fluctuations. Combination of Nivolumab and Ipilimumab are used in the management of melanoma [28]. Nivolumab are investigated in different types of tumors including gastric cancer (phase III), GBM (phase III), acute myeloid leukemia (AML) (phase II), anal canal (phase II), cervical cancer (phase II), colon cancer (phase II), HL, NHL (phase II), nasopharyngeal carcinoma (phase II), pancreatic cancer (phase II) [4]. Nivolumab is one of important Immune checkpoint inhibitors in HCC clinical trials. Nivolumab's pre-clinical findings has moderate effect and its clinical efficacy has a strong influence on improvement of survival. It is used for the first line treatment of melanoma in phase 3 clinical trial. Nivolumab's control arm is Dacarbazine. Melanoma response rate of Nivolumab is approximately 40 vs. 13.9%. Nivolumab is used in treatment of NSCLC as pretreated with response rate about 32 vs. 11% in phase 3 clinical trial and the control arm is investigator's choice chemotherapy [1].

3.6 Atezolizumab

Atezolizumab is a humanized Fc-engineered IgG1 monoclonal and binds to PD-L1. Atezolizumab promote neither activate antibody-dependent cell-mediated cytotoxicity (ADCC) nor complement-dependent cytotoxicity (CDC). Also, Atezolizumab blocks the interaction with PD-1 and B7.1 receptors on tumor cells. Recent study shows that the best dosage for metastatic urothelial carcinoma and metastatic NSCLC is 1200 mg every 3 weeks. Also later study on dose-escalation in phase 1 indicates dosage of Atezolizumab is about 0.01–20 mg/kg based on body weights [32].

3.7 Durvalumab

Durvalumab is a humanized Fc-engineered IgG1 monoclonal and binds to PD-L1. Durvalumab promote neither ADCC nor CDC, and avoids the ability of toxicity caused by it does not have attraction to joining PD-L2. Recommended dosage of Durvalumab is 10 mg/kg each 2 weeks in carcinoma of urothelial. Proposed concentration in metastatic urothelial carcinoma is about 50 μg/mL. Recommended fixed dosage regimen of Durvalumab is 1500 mg every 4 week or 750 mg every 2 week. This regimen indicates similar overall pharmacokinetic exposure based on body weight [33].

3.8 Avelumab

Avelumab is a fully human IgG1 monoclonal antibody and has short half-life for about 3.9–4.1 days compare to Nivolumab which is about 12–20 days, Pembrolizumab with half-life of 14–22 days, and Atezolizumab with half-life of 21 days. Avelumab shows the reduction in clearance similar to Nivolumab and Pembrolizumab during long treatments. The investigation of avelumab on metastatic Merkel cell carcinoma after 1 year of follow up has shown that avelumab can be effective in treating advance Merkel cell carcinoma due to 33.0% overall response rate (ORR) and 11.4% to complete response rate. The dosage is used in that study was 10 mg/kg every 2 weeks. Also, studies in phase 1 have shown that this drug can also be effective in patients with platinum-refractory metastatic urothelial carcinoma cancer due to 17.3% ORR [24, 34–38].

4. Second group of immunotherapy medication

Next-generation of novel therapeutic target include VISTA, LAG-3, TIGIT, and TIM-3 inhibitors. Also, another potential checkpoint is p-selectin glycoprotein ligand-1 (PSGL-1) which regulates T-cell responses in tumor microenvironment (TME). CTLA-4 and PD-1 are co-target receptors which they are responsible for supporting overall immune self-tolerance. However, TIGIT, LAG-3, and TIM-3 receptors influence on NK and CD8+ T-cell. Treg cell suppressive influence and improving CD8+ and NK cell activity inside malignancy tissues is revoked by synergizing their corresponding blockade. Thus, synergizing of first- and second generation inhibitors provoke immune system to have beneficial response against malignancies [2, 39–41].

4.1 T-cell immunoglobulin-3 (Tim-3)

Tim-3 is expressed on IFNγ producing CD4+ T helper 1 (Th1) and CD8+ T cytotoxic 1 (Tc1) T-cells. Also, Tim-3 is expressed on Treg cells and on innate immune cells (DC, NK cells, and monocytes). Co-inhibition of Tim-3 and PD-1 is more beneficial than PD-1 alone inhibition in anti-tumor effector functions. Tim-3 shows the dysfunction of CD8+ T-cells in cancers. Co-inhibition in Tim-3 and PD-1 has greater effects in managing melanoma, NSCLC, and NHL [37].

4.2 T-cell immunoglobulin and ITIM domain (TIGIT)

T-cell immunoglobulin and ITIM domain (TIGIT) Ligand (CD155 and CD112) are expressed in tumors cells. Negative TIGIT up regulate anti-tumors activities. Dysfunctional phenotype among CD8+ TILs is produced by co-expression of CD8 plus TIGIT+ TILs with PD-1, Tim-3, and Lag3. Co-inhibition of TIGIT with PD-1 increased proliferation, cytokine production, and degranulation In CD8+ TILs from melanoma patients [37]. Moreover, TIGIT synergies with Tim-3 to improve anti-tumor responses. So, both co-inhibition of TIGIT with PD-1 or TIGIT with Tim-3 induce anti-tumor effects. In addition, TIGIT are expressed on tumor infiltrating Treg. Restrictive phenotype of Treg cell is provided by the TIGIT+ Treg in tissues with malignancy cells. Notably, CD8+ T-cell function (direct suppression) and promotion of Treg function (indirect suppression) can suppress anti-tumor immunity by TIGIT [37].

4.3 B-cell and T-cell lymphocyte attenuator (BLTA)

B-cell and T-cell lymphocyte attenuator (BTLA) is an immunoglobulin-like molecule expressed on different cells such as on B-cells, T-cells, NK cells, and APCs. BLTA is a section of CD28 family. BLTA plays a major role in early T-cell regulation and provides early T-cell response gene. Combination of BLTA and herpes virus entry mediator (HVEM) induces reduction of T-cell proliferation and cytokine production. Melanoma cells are expressed HVEM. The combination of BTLA and HVEM inhibits the expansion and IFNγ production. Also, BLTA is related to restricted T-cell expansion. Inhibition of BTLA, PD-1, and TIM3 together increase IL-2. Inhibition of BTLA, PD-1, and TIM3 can restore T-cell dysfunctions. After the BTLA and HVEM interconnections, T-cell activation and level of IFNγ decreases [13].

4.4 V-domain Ig suppressor of T-cell activation (VISTA)

V-domain Ig suppressor of T-cell activation (VISTA) is a powerful suppressor of T-cell [13] which is expressed by hematopoietic tissues and infiltrating leukocytes.

VISTA is predominantly found on leukocytes inside tumors and myeloid hematopoietic section 140. Like PD-L1, it promotes suppression of CD4 and CD8. VISTA also has long-lasting kinetics which can induce the reduction of cytokine production such as IL-10, TNF-alpha, and IFNγ. VISTA inhibition increase the frequency of tumor-infiltrating effector T-cells by combining to a specific antibody. Thus this combination inhibit tumor growth. VISTA can increase overall survival by combining to an agonistic CD40 antibody, TLR agonists, and tumor antigen peptides [13].

4.5 CD160

CD160 is a glycosyl-phosphatidyl-inositol (GPI) which is expressed on CD8þ T-cells, NK cells, and NK-T cells. CD160 inhibition induces T-cell proliferation and cytokine production 147. Also, CD160 is a ligand for HVEM. The combination of CD160 and HVEM promote the suppression of T-cells. So, CD160 is an inhibitory checkpoint for T-cells [13].

4.6 CD244

CD244 is a immunoglobulin which can regulate and activates the lymphocytes. In addition, CD244 can stimulate both T-cell and NK cells. NK cytotoxicity is inhibited opposed the expression of CD48 by CD244. CD244 can provide both suppression and activation of T-cell by cross linking, related to CD244 level of expression and adaptation of intracellular molecule. Recent study shows that CD244, LAG-3, and PD-1 is reduced in tumor-infiltrating antigen-specific CD8þ T-cells by herpes virus glycoprotein (GD) adjutant vaccine [13].

5. Passive immuno-therapy

With the exception of immuno-suppressants, many other important therapies are developing immunization that can be divided into active or inactive Immunotherapy with respect to host immunity when detecting anti-tumor responses. Active immuno-therapies have correlation with capacity of anti-tumor attack of T-cell. However, passive Immunotherapy includes inherent anti-tumor properties of adaptive T-cell therapy [1, 41].

5.1 Tumor-targeting monoclonal antibodies (mAbs)

MAbs have different effects on immune cells. First, mAbs can change the receptor's signaling role which malignant cells expressed them. Second, they neutralize the signals which malignant cells or stromal components or neoplastic lesion provided them. MAbs identify cancer cells due to tumor associated antigen (TAA) expression which expressed by transformed cells [39, 42]. Another anti-cancer immuno-therapies against activatory checkpoint receptors include anti-CD137 or anti-CD40 which are being tested in clinical trials [1]. MAbs Cetuximab blocks signaling pathways which determine neoplastic cells' survival or progression. Also Cetuximab is approved for the treatment of head and neck cancer. In addition, it is used in managing colorectal carcinoma [9, 39, 43, 44]. Naked mAbs such as Tigatuzumab activates murderous receptors of malignant cells. Gemtuzumab ozogamicin is an anti-CD33 Calicheamicin. Gemtuzumab ozogamicin binds to a TAA-specific mAbs. It use for acute myeloid leukemia patients [38]. CD20-specific mAb Rituximab is complement-dependent cytotoxicity. Rituximab is activated by TAA-specifics mAbs. Also, naked TAA-specific mAbs activates ADCC and

antibody-dependent cellular phagocytosis [39, 45, 46]. A recent study shows that Rituximab has beneficial influence on chronic lymphocytic leukemia, and NHL [39, 46, 47]. Blinatumomab is a CD19- and CD3 bispecific T-cell engagers (BiTE) which is chimeric proteins includes of two single-chain changeable fragments from mAbs. BiTE has two fragments, one of them target a TAA and another target T-cell surface antigen. Blinatumomab is approved for treatment of B-cell acute lymphoblastic leukemia. MAbs and BiTE should be considered active immuno-therapeutic or passive immun0-therapeutics. This implying depends on host immune responses. For example, Cituximab can block epidermal growth factor receptor (EGFR) signaling and also can induce ADCC. In addition, Cituximab can mediate the effects of immuno-stimulatory [39, 48]. Bevacizumab is approved for management of glioblastoma multiform, cervical carcinoma, renal cell carcinoma, and lung cancer due to anti-angiogenesis effects. But, Bevacizumab induces tumor infiltration via lymphocyte B and lymphocyte T. In addition, Bevacizumab blocks CD4+ CD25+ FOXP3+ regulatory T-cells [39, 48, 49].

5.2 Summary of anti mAbs indications

Alemtuzumab's indication is chronic lymphocytic leukemia. Bevacizumab's indications are colorectal carcinoma, lung carcinoma, renal cell carcinoma. Brentuximab vedotin indications are anaplastic large cell lymphoma and HL. Blinatumomab indication is acute lymphoblastic leukemia. Catumaxomab indications are malignant ascites in patients with epithelial cell adhesion molecule (EPCAM) + cancer. Cetuximab indications are head and neck cancer and colorectal carcinoma. Denosumab indications are breast carcinoma, prostate carcinoma, and bone giant cell tumors. Gemtuzumab ozogamicin indication is acute myeloid leukemia. Ibritumomab tiuxetan indication is NHL. Panitumumab indication is colorectal carcinoma. Pertuzumab indication is breast carcinoma. [38]. Obinutuzumab indication is chronic lymphocytic leukemia. Ofatumumab indication is chronic lymphocytic leukemia. Ramucirumab indications are gastric or gastroesophageal junction adenocarcinoma. Rituximab indications are chronic lymphocytic leukemia and NHL. Siltuximab indication is Multicentric Castleman's disease. Tositumomab indication is NHL, and Trastuzumab indications are breast carcinoma, gastric or gastroesophageal and junction adenocarcinoma [38].

5.3 Oncolytic viruses

Oncolytic viruses have potential anti-neoplastic effects and can inherent cytopathic effects. Productive viral infection up regulates the mortal overcharge of cellular metabolism. Oncolytic viruses are lethal for host cells due to endogenous or exogenous gene products, and are approved by US food and drug administration (FDA) [39, 50].

5.4 Oncorine H101

Oncorine H101 is oncolytic viruses. Oncorine indication is head and neck cancer. The mechanism of action is selective lysis of malignant cells [38].

6. Immune oncology biomarker and immune response

Biomarkers have different purpose and are seen as a pre-existing anti-tumor in certain developing tumors. Also, response to immune treatments can

provide specific biomarkers [48]. When blockade of the PD-1/PD-L1 checkpoint response increase, PD-L1 expression can be seen in the TME. The high level expression of PD-L1 is related with a higher response rate and its expression increases survival [48]. Immunotherapy can exacerbate tumor lymphocytes (TILs), which illustrates antitumor immune response [48]. CD8 T-cells are associated with tumor regression after stopping of PD-1/L1 in melanoma metastasis. Increased immunogenicity of a tumor shows an increasing of tumor mutational load and neoantigen [49]. High mutational burdens increase survival than low load. Mutational load and neoantigens have been shown in many type of advance tumors including melanoma, NSCLC, and colorectal carcinoma. The investigations on colorectal carcinoma illustrate higher tumor-infiltrating lymphocytes and smokers response which is better than nonsmokers (adenocarcinomas) [1]. Immuno-stimulatory or immune inhibitory cytokines existence in the microscopic environment of the tumor forecast susceptibility or resistance. There are several methods for research in the microscopic environment of the tumor including immuno-histochemistry, immuno-fluorescence, whole-exome sequencing, transciptome analysis, proteomics, flow cytometry and others [48]. Type I interferon-based transcriptomic signatures has beneficial effect in metastatic melanoma. However, it may originally be used for other types of tumors [1]. Several investigations on PD-1/PD-L1 checkpoints indicate that TME PD-L1 (TME cell types express PD-L1) expression is significantly related with response [29]. Tumors with negative PD-L1 are resistance to therapy since tumor or immune cell must have PD-L1 for immune checkpoint therapy [29]. Alone PD-L1 (B7-H1) expression cannot adequately predict the Immunotherapy response. So, adding PD-L1 with another parameters (CD8+ T-cells or an IFNγ gene signature) improves predictive value [48].

6.1 Imaging biomarker

There are two main approaches for imaging in clinical oncology including anatomic and functional imaging. Anatomic change fluorescence and bioluminescence are the most useful imaging techniques. In addition, magnetic resonance imaging (MRI) improves contrast and increase resolution of anatomic images. Also, MRI can improve range of functional measure. Dynamic contrast-enhanced MRI can indicate tumor perfusion and permeability of cell membrane. Diffusion-weighted MRI demonstrates the access of drug by parameters such as rate and distance of water molecule. Recent study evaluates immunotherapy by using cells labeled with either super paramagnetic iron oxide particles or perfluorocarbon nanoemulsions in MRI-based cell follow [51, 52]. Detecting biochemical markers in tumors is possible by single-photon emission computed tomography (SPECT) and PET. These two mature imaging techniques has beneficial effects such as high-resolution images, the potential to quantify metabolic activity for corrects attraction of therapeutic influences [52]. The investigations on lymphoma and solid tumors shows that 18F-FDG-PET imaging which is oncologic nuclear imaging is very useful for disease response evaluations. But, there are few important problem with 18F-FDG-PET such as the distinction between neoplasm and infectious or inflammatory processes. SPECT provide high resolution similar to PET. However, beneficial advantage of SPECT in comparison with PET is ubiquity of SPECT cameras, reduced cost structure, increased logistics for imaging caused by longer half-lives of the radionuclides, and a greater number of radionuclides available for labeling. 99mTc-methyldiphosphonate (99mTc-MDP) is the most useful SPECT agents in imaging of advance osteoblastic bone cancer. Real metastases are not detected by bone scan, while the reaction of the skeleton

to metastases can be found [52, 53]. Also, another SPECT agents which they are useful for different cancers including using 123I-metaiodobenzylguanidine (123I-MIBG) in neuroblastoma, using 111In-pentreotide in patients with neuroendocrine tumors, and 123I-sodium iodide (NaI) for thyroid distinction between expected post immuno-therapeutic results. The most frequent use of PET agent is 18F-fluorothymidine (18F-FLT) which is a marker for proliferation of the cells. 18F-fluorothymidine (18F-FLT) improves the differentiation between tumors and false positive rate associated to infections and inflammations [52]. 18F-FLT has some limitations in comparison with 18F-FDG-PET such as reduction in signal to background ration. Also, 18F-FLT shows background structures such as bone marrow, which cannot show the activity of the tumors and reduces the identification of tumors. Furthermore, 18F-FlT gathers in area of infection and inflammation lesser than 18F-FDG [54].

7. Immune response

Genomic factors play an important role in responding to Immunotherapy. Across several mechanisms, viral proteins have influence on intercommunication alongside T-cells and malignancy. For example anti-tumor cytotoxic activity of the NK cells is increased by hidden cytomegalovirus [55]. In addition, PD-L1 expression is provoked by EBV in NHL and other EBV+ cancers [53]. one of the most responsive cancer to checkpoints inhibitor is HL. Also, HL has high level of PD-L1 expression. PD-L1 expression is reduced in HPV+ tumors; But, T-cell infiltration is increased in HPV+ tumors. Therefore, an important biological biomarkers for Immunotherapy is the presence of viral proteins [56]. Recent study shows that Merkel-cell polyomavirus positive tumors have higher PD-L1 expression (71 vs. 25%). Response rate in virus positive tumor is about 65 vs. 44% higher than virus negatives tumors [48].

8. Combination therapy

Combination therapy can increase response rate, efficacy and improve multiple components of T-cell anti-tumor responses. It has been reported that, Nivolumab + Ipilimumab are beneficial against melanoma. But, this combinations may have many serious side effects such as hepatitis, colitis, pneumonia. Bevacizumab combine with interferon-alpha to manage renal cancer. The combination of Elotuzumab and Dexamethasone and Lenalidomide is useful to control multiple myeloma [7, 59]. Combination of Nivolumab and Pembrolizumab is prescribed for managing squamous and non-squamous NSCLC [4, 33].

8.1 Binary checkpoint inhibition

Combination of Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4) provide total two-year survival in 79% of cases in metastatic melanoma. Also this combination has 53% objective response rate in metastatic melanoma. Recent study shows combinations of Nivolumab and Ipilimumab has 61% objective response rate. However, Ipilimumab alone has 11% objective response rate. Totally, recent study shows 22% remission [2]. Also, later investigations shows that the combination of anti-PD-1 and CTLA-4 stimulate T-cell more than anti-CTLA-4 alone. In combination of PD-1, CTLA-4 and VISTA blockade checkpoint is demonstrated the stimulation of T-cell [2].

8.2 Checkpoint inhibitor and mAbs

Combination of Tremelimumab (anti-PD-1) and a CD40-agonist mAb has 27% objective response rate, 26 months overall survival. T-cell antigen 4-1BB is targeted by mAb's, and improves T-cell stimulation [57]. Combination of 4-1BB agonists with PD-1 blockade has notable results in rejection in murine model with colon adenocarcinoma. This combination therapy led to increase the level of IFNγ-producing CD8+ and CD4+ T-cells in comparison with monotherapies. Efficacy of OX40 agonist is decreased by PD-1 inhibitions. Also, PD-1 blockade causes reduction of CD4+ and CD8+ lymphocyte infiltration and causes 30% breast tumors remissions [58].

8.3 Epigenome regulator

Epigenome regulator is coupled with checkpoint inhibitor, and includes an inhibitor of histone deacetylases (HDAC) or DNA methyl-transferase (DNMT). HADC typically associated with the cancer process [59]. Immune checkpoint management mechanisms contain covalent modifications, microRNAs (miRNAs), and long noncoding RNAs (lncRNAs), and histone modifications. DNA methylation and histone acetylation have the most effects in management of growth and activation of T lymphocyte. Inhibition of HDAC promotes tumor death. Inhibition of HDAC provokes tumor death by different pathway such as reactive oxygen species (ROS) and apoptosis. HDAC inhibitor is prescribed for different type of malignancies including leukemia, gastric carcinoma, NSCLC. HDAC inhibitors have several complications including lymphopenia, leukopenia, neutropenia, and thrombocytopenia. Combination therapy of HDAC and DNMT inhibitors with other immunological agents is used for more efficacy. For example, Entinostat is combined with Nivolumab and Ipilimumab for managing metastatic breast cancer. Also, Entinostat with Pembrolizumab is used for solid tumors, metastatic uveal melanoma and NSCLC. Mocetinostat and Durvalumab are used for managing solid tumors [60–62].

8.4 Selective therapy with checkpoint inhibitor

Checkpoint blockers coupled with receptor and non-receptor tyrosine kinases (TK) play major roles in tumorigenesis. The angiogenesis provides growth factor VEGF and restricts T-cell infiltration through the tumor endothelium. In addition, angiogenesis promotes myeloid-derived suppressor cells (MDSCs) and Treg cells inside tumors. Combination of Bevacizumab (a VEGF inhibitor) with Ipilimumab can control 67% in metastatic melanoma. In addition, this combination can induce T-cell activation inside tumors with approving toleration level. It is currently attempting to coordinate anti-PD-1/PD-L1 MABs with VEGF inhibitor for even greater effectiveness [60]. Imatinib (TKI) with an anti-CTLA-4 mAb decrease Treg cell. Tumor volume is decreased 50% by CTLA-4 and Indoleamine 2,3-dioxygenase (IDO) blockade combination during 80 days [60]. Tumor volume is decreased 50% by CTLA-4 and IDO blockade combination during 80 days [60]. Combination of PD-1 and IDO blockades has favorable effects on advanced melanoma [2].

8.5 Adaptive T-cell therapy (ACT) with checkpoint inhibitor

Adaptive T-cell therapy induces anti-tumor stimulation. CD19-specifics chimeric antigen receptor (CAR) T-cell therapies provide 90% revocation of which 67% of them have response following 6 months in acute lymphoblastic leukemia patients. In addition, more than 53% complete response rate has shown in B-cell lymphoma [61].

8.6 Nanoscale coordination polymer (NCP) with checkpoint inhibitor

Combination of anti-PD-l1 (Pembrolizumab) and nanoscale coordination polymer (NCP) combination increase CD8+ T-cells in tumors. Survival rate is increased by antiPD-1 checkpoint inhibitors and agonistic anti-OX40 antibodies. Anti-OX40 antibodies encourage the stimulation of elevated T-cell due to increased release of IFNγ and increased CD8+/Treg cell ratio [59]. It has recently been shown that presentation of antigen is increased by synthetic polymeric nanoparticle PC7A. Also, flexible nanovaccin platform carry antigens to lymph nodes. The combination of PD-L1 inhibitor and laser light and gold nanostars, which they are called photodermal nanotherapy, can manage advance metastatic bladder malignancy [2].

9. Conclusion

Immunology has changed the way of cancer treatments and control. Primitive immunotherapy with checkpoint inhibitors provides beneficial results. However, the combination of checkpoint inhibitor with other immune target agents provide new generation of immune-oncology treatments. Knowledge about immunological checkpoints, immuno-oncology biomarkers, immune response, therapeutic resistance and combination therapy helps us in the process of cancer diagnosis/follow-up, and imaging during immunotherapy helps to better understand the patients' immune response.

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