Review Article

Review of Current Trends and Research on Clinical Immuno-oncology

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ABSTRACT

This article provides a comprehensive review of current trends and research in clinical immune-oncology, focusing on the evolving landscape of cancer treatment through the lenses of cytokines, artificial intelligence (AI), and the tumor microenvironment (TME). The global burden of non-communicable diseases, particularly cancer, underscores the critical need for innovative approaches in clinical oncology. The article focuses on cytokines, highlighting their pivotal role in cancer treatment, and the promising potential of modified cytokines, adoptive T-cell transfer, and fourth-generation CARs. Clinical trials combining cytokines with established drugs underscore the progress in cancer immunotherapy. AI has transformed the landscape of clinical oncology, particularly in predicting individual cancer risks and enabling targeted interventions. Deep learning algorithms are discussed as a powerful tool for learning intricate patterns in vast datasets. The article also discusses the intricate world of the TME, emphasizing its role as a complex ecosystem influencing a tumor's fate and metastatic potential. The article underscores the potential of these advancements in revolutionizing cancer treatment but calls for continued research and concerted efforts to address challenges and ensure seamless integration of these innovations into clinical practice.

Keywords: Cancer research, immune-oncology, cytokines studies, AI in clinical oncology, TME research.

INTRODUCTION

Clinical trials play a critical role in discovering and developing new therapies. Over the past decade, clinical trials have evolved widely to modify biological drivers and therapeutic chances[1]. The current trend in clinical trials involves a shift from evaluating cytotoxic agents to emphasizing molecularly targeted agents and immuno-oncology compounds[2].

Worldwide noncommunicable diseases are noted for 71% of the deaths and new cancer cases (18.1 million), breast cancer was the most common case in the world (11.7%) and suppressed lung cancer(11.4%) reports, prostate (7.33%), liver(8.3%)[3] As per the GLOBOCAN series overall, an estimated 12.7 million new cancer cases were found and 7.6 million cancer deaths were noted in 2008 [4]. In Europe, cancer is the most public concern disease; almost 25% of global cases occur on the continent[5]. In India cancer is one of the leading diseases (9%) [6].

In the realm of clinical oncology, the intricate interplay of cytokines, artificial intelligence, and the tumor microenvironment stands at the forefront of innovative approaches to understanding and treating cancer[7]. Cytokines, characterized as polypeptides or glycoproteins with a molecular weight of less than 30 kilodaltons[8], play a pivotal role in providing growth and anti-inflammatory signaling to various cell types[9]. Their potential in cancer treatment has been explored through animal murine cancer models[10], with specific cytokines like IFN-α and IL-2 showing efficacy in diseases such as hairy cell leukemia and metastatic renal cancer[11].

The evolving landscape of immunotherapy, with a wide-ranging potency against various cancers[12], introduces novel concepts like adoptive T cell transfer and fourth-generation CARs (Chimeric Antigen Receptors) that aim to recognize and destroy malignant cells[13]. Modified cytokines, undergoing clinical trials, are combined with drugs like mepolizumab, nivolumab, and ipilimumab to showcase response rates in cancer immunotherapy[14]. In this context, the fusion of apolipoprotein with cytokines and the first-in-human trials utilizing recombinant human IL-15 highlight promising advancements in the field[15].

On another frontier, artificial intelligence (AI) has emerged as a transformative force in clinical oncology[16]. With the ability to predict individual cancer risks, AI facilitates targeted screening and early interventions[17]. Deep learning algorithms, a novel method in machine learning, empower AI to learn intricate patterns in vast datasets. The integration of AI in cancer treatment decisions provides incremental benefits, addressing critical touchpoints for both oncologists and patients. However, challenges persist in translating these advancements into clinical practice, emphasizing the need for models with clinical validity, utility, and usability[18].

The tumor microenvironment (TME), a complex ecosystem comprising tumor cells, immune cells, and non-immune cells, plays a decisive role in determining a tumor's fate and metastatic potential[19]. Efforts to include immune parameters in prognostic tools demonstrate promising outcomes, particularly with CD8+ T lymphocytes recognized as anti-tumor immune cells[20]. Genetic

mutations shaping the immune microenvironment, coupled with advancements in sequencing and computational techniques, reveal the diverse subclones within tumor masses[21]. Melanoma studies, correlating with higher densities of tumor-infiltrating lymphocytes, showcase the potential for improved prognostic tools like Immunosorbent[22].

As we explore the subtleties of cytokines, AI applications, and the tumor microenvironment, we unravel the intricacies that hold the promise of revolutionizing the landscape of clinical oncology[23]

2. CYTOKINES IN CLINICAL ONCOLOGY:

Cytokines are polypeptides or glycoproteins that provide growth, and anti-inflammatory signaling to cell types, and their molecular weight was less than 30 kilodaltons [24]. Cytokines administered parenterally to control the immune response were subjected to efficacy in animal murine cancer models[25].

Ifn-α:

IFN-α for hairy cell leukemia and interleukin-2 for metastatic renal cancer[26]. Immunotherapy has wide potency for effective treatment for many cancers. Blockade of CTLA4 and programmed cell protein may give ideas to future approaches for immuno-oncology therapy[27]. In this context, the adoptive T cell transfer is a new transfusion method for the infusion of lymphocytes to treat tumors [13]. In the fourth generation of CARs, adoptive cell therapy was used to recognize malignant diseases and destroy the cancer cells[28]. The pro-inflammatory cytokines also contribute to cancer immunotherapy and are used to deactivate every phase of the cancer immunity cycle[29,30]. According to in vivo studies the apolipoprotein enhances the immune responses more than IFNα or ALF[31]. The modified cytokines are used in clinical trials with a combination of drugs such as mepolizumab, nivolumab, and ipilimumab to show response rates in cancer immunotherapy[32].

Il-2:

the mutated IL-2 is fused to target the cytokine therapy in cancer TME[33]. IL-2 is a crucial cytokine for promoting natural killer and T cell expansion and is used in adoptive transfer protocols for cancer treatment. However, its toxic profile hinders systemic administration. Second-generation therapies are being developed to improve pharmacokinetic and pharmacodynamic profiles. The IL-2 receptor complex consists of medium and high-affinity receptors[34]. The pertuzumab amunaleukin was also the IL-2 variant fused to the carcinoembryonic antigen [33].

Il-15:

The IL-15 was produced by the activated myeloid cells and importantly, it was an essential need for NK cells and CD8+ T cells ontogeny[35]. the IL-15 also induced cell proliferation, the cytotoxic effect, and one of the cytokines IFN-γ was released for action[36]. It plays a crucial for immune response in cancer therapy, according to research IL-15 produces the anti-tumour effect mediated by NK and T-cells. Unlike IL-12, IL-15 does have a response to binding to CD25[37,38]. The study conducted the first-in-human trial using recombinant human IL-15 (rhIL-15) produced in Escherichia coli and the trial involved daily intravenous bolus infusions of varying doses of IL-15 over 12 consecutive days in patients with metastatic malignant melanoma or metastatic renal cell cancer[39].IL-15 is a cytokine that has a promising tumor[40]. The IL-15 agonist RLI has a more significant effect and its reduced toxicity and improvement in the action of the disialogangliosi(GD2) showed robust anti-cancer activity in murine models of cancer disease[41]. The fusion of apolipoprotein with interleukin -15 acts as a therapeutic carrier for cytokines[42].

Il-21:

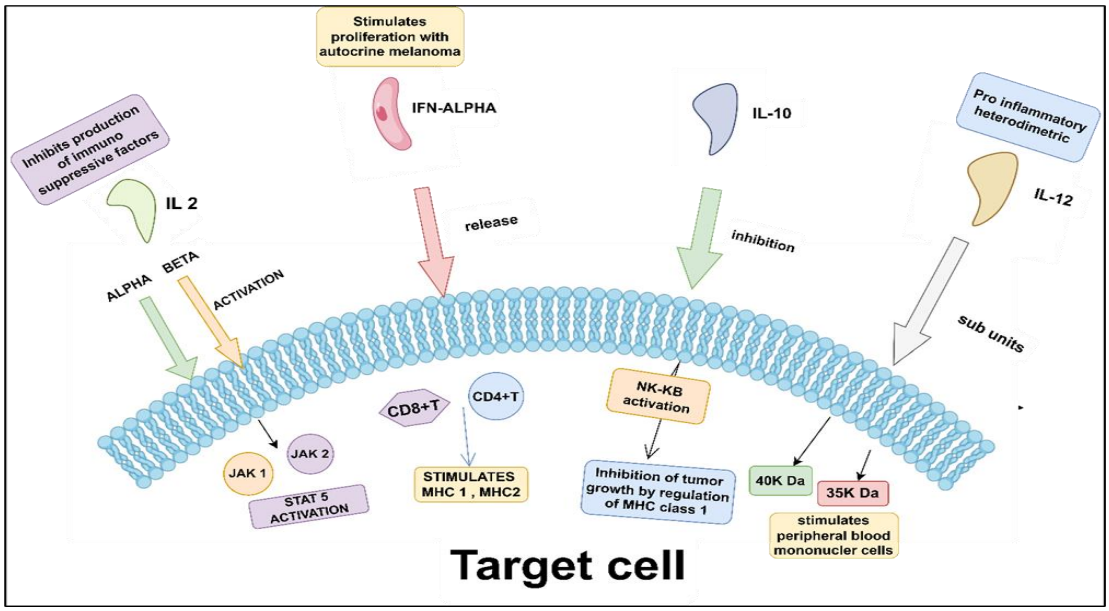
Interleukin-21 was another cytokine that originated from IL-2 [43] and it was tested alone in a clinical trial (NN0281614) of metastatic melanoma cancer studies and with a combination of sunitinib (NCT00617253) for stage IV renal cell carcinoma patients and combination of oral sorafenib (NCT00389285) for metastatic renal cell carcinoma studies. The recombinant IL-21 and rituximab combination was tested on 21 patients with relapsed small chronic lymphocytic leukemia and was well tolerated and produced active effects[44]. However, the clinical cytokines are still needed to progress for combinations.

Il-10:

The IL-10 was originally isolated from T Helper cells and it was used to minimize the side effects and control the immune response against Leishmania major[45]. IL-10 is an immunosuppressive cytokine that can reduce the antigen activity of the dendritic cell population[46] and inhibit cytotoxicity [47].

Il-12:

IL-12 is a 70kDa heterodimeric cytokine composed of the p35 and p40 subunits[48]. And is mainly produced by macrophages, B, and DC cells[49]. In addition, stimulation of CD40 on human monocytes produces IL-12, and activation of T cells expressing CD40L results production of IL-12[50]. In preclinical studies, the administration of recombinant IL-12 produced an active anti-tumor effect in rat models[51] and the eradication of large tumors was successful by IL-12 in preclinical studies[52]. IL2 is a growth factor for CD4+ T cells and is involved in adaptive immunity. It is associated with disease progression in cancer and has been approved for treating metastatic renal cell carcinoma and melanoma. IL10 is highly immuno-suppressive and can inhibit tumor development and progression. TNFα, a pro-inflammatory cytokine, is involved in inflammation-associated carcinogenesis and could be a potential cancer therapeutic. IL-12, a pro-inflammatory cytokine, is essential for the production of IFNγ and is decreased in many cancer types, particularly in late stages with advanced disease.



ARTIFICIAL INTELLIGENCE IN CLINICAL ONCOLOGY:

In recent years, AI has been used to predict an individual's cancer risk, enabling effective and efficient targeting of screening and early interventions. there's been a renewed interest in AI applications in medicine, fuelled by advancements in deep-learning algorithms, hardware, and growing data for clinical decision-making. Here, we discuss the key concept of advanced artificial intelligence applications in oncology [53,54].

Deep learning is a newer method of machine learning used to learn neural networks [55]. Touchpoints in cancer treatment involve critical decisions for oncologists and patients, with AI providing incremental benefits. Ideal use cases have significant unmet needs and large datasets, requiring robust annotation for supervised machine learning[56].

In Narrow tasks, AI was used to predict the risk and help in prevention[57]. They are increasing data streams and advanced computer algorithms to enhance clinical oncology through narrow applications, interacting at specific touchpoints. However, challenges remain in clinical translation. Successful models use large-scale datasets and further development should focus on clinical validity, utility, and usability[58].

TUMOR MICROENVIRONMENT:

The tumor microenvironment (TME) is a complex ecosystem involving tumor cells, immune cells, and non-immune cells. The immune cell component determines a tumor's fate and invasive and metastatic ability[59]. Efforts to include immune parameters in oncology prognostic classification tools show promising results[60]. CD8+ T lymphocytes are anti-tumor immune cells that recognize and kill tumor cells but must be primed and educated by professional antigen-presenting cells before they can effectively function[61]. Immune cells, including tumor-promoting M2 macrophages and myeloid-derived suppressor cells, can promote tumor progression through cell proliferation, vascularisation, ECM deposition, and migration, while also inhibiting the in situ immune response[62,63]

Genetic mutations, such as single-base substitutions and chromosome translocations, are the basis of developing neoplastic lesions. [64] These mutations can be induced by various stressors, such as carcinogens, radiation, or chronic inflammation[65]. These mutations shape the immune microenvironment through peptide epitopes recognized by CD8+ T cells, promoting infiltration by cytotoxic T lymphocytes[66].

Advances in sequencing and computational techniques have led to the understanding that tumor masses are composed of different subclones with different immunogenic potentials[67].In the tumor microenvironment, Melanoma has been linked to a higher density of tumor-infiltrating lymphocytes (TILs), resulting in a lower incidence of lymph node metastasis and longer disease-free survival[68]. Studies have shown that a lower TIL grading correlates with lower DFS, supplementing other prognostic factors 69,70.

An immunohistochemistry-based grading score system called Immunosorbent has been developed to validate the prognostic significance of TILs in colorectal cancer (CRC)[71]. The system quantifies CD3+ and CD8+ cells in the tumor and scores them as low, intermediate, or high. An international consortium has scored over 3500 CRC patients using this system, finding it superior to the classical TNM system[72]vali. However, the system faces challenges in clinical practice, including the need for an automated system for IHC staining and digital pathology software[73].

CONCLUSION

This summary discusses the evolving landscape of cancer treatment, focusing on the role of cytokines, artificial intelligence (AI), and the tumor microenvironment. Cytokines, such as IFN-α, IL-2, IL-15, IL-21, IL-10, and IL-12, are used in immunotherapy, with strategies like adoptive T

cell transfer and fourth-generation CARs promising for identifying and eliminating malignant cells. AI can predict individual cancer risks and enable targeted interventions, but challenges in clinical validity, utility, and usability need to be addressed. The tumor microenvironment, a complex interplay of cells and factors, is a critical determinant of a tumor's fate and metastatic potential. Advances in sequencing and immune parameters are being used to improve prognostic tools, but challenges in clinical application persist. The article concludes by highlighting the potential of these advancements in cancer treatment, emphasizing the need for interdisciplinary collaboration and further research to improve patient outcomes and understanding of immune-oncology.

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