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PHARMACEUTICAL SCIENCE BRINGS GENETICS AND IMMUNOLOGY TOGETHER TO EVOLVE A NEW DIMENSION IN TREATING CHILDHOOD CANCER: A REVIEW

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ABSTRACT: Surgery, chemotherapy and radiation therapy has been the cornerstone of cancer management for decades. Since a decade or so, targeted therapies by way of Imatinib and Trastuzumab arrived that specifically target cancer cells and reply on specific molecular changes to identify them. These are in fact the standard treatment at present in several forms of cancer. But now in recent times, the fifth pillar of cancer treatment has gradually emerged where the patient's immune system is hired to address and kill his own cancer cells. One such strategy for treatment is involving engineered immune cells of a patient to identify and kill his own tumours. Although this approach, often called adoptive cell transfer or ACT is now limited to small tests and trials, these are seen are true silver bullets in the days to come in treating cancer. This review discuss this new development in pharmaceutical science were living drugs are emerging through high end genetic engineering that exploit the specificity of an antibody and the unique cytotoxic effect of T cells to address cancer.

INTRODUCTION: World Health Organization (WHO) defines childhood as 0-14 year group. Amongst all form of cancers found in this age group, leukemia happens to be the most important and significant one. With increasing level of research on this form of cancer across the globe the present understanding on leukemia has enhanced greatly in the recent decade. Despite the marked similarity at immunological and morphological level, dramatic chromosomal and molecular differences has immensely contributed to the modern classification of leukemia. This has in turn contributed to superior mode of treatment of this category of diseases [1].

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Acute Lymphoblastic Leukemia: A form of blood cancer that is highly prevalent in children. Acute lymphoblastic leukemia or acute lymphocytic leukemia or acute lymphoid leukemia (ALL) is an acute category of leukemia which is commonly known as the cancer of the white blood cells. In this disease, there is over production of immature white blood cells that eventually accumulate. Such cells are also known as lymphoblasts [2].

The over production of these lymphoblasts occur within the bone marrow that in turn causes inhibition of normal cells such as the red and white blood cells as well as platelets. It also infiltrates into other organs causing organ damage. ALL is most often encountered in childhood stage, and the incidence is the highest at 2–5 years of age.

Yet another high rate if incidence is encountered at old age also [3]. The most common symptom of this disease is a reduced production of functional blood cells since leukemia utilizes bone marrow resources that are otherwise used to manufacture new, functioning blood cells [1]. The disease is characterized by fever, a high chance of infection such as that of bacterial source like pneumonia because of neutropenia. The disease is associated with shortness of breath, pain in the chest, cough, vomiting, changes in bowel or bladder habits, increased tendency to bleed because of thrombocytopenia and symptoms of anemia, including pale look, tachycardia or high heart rate, fatigue, and headache [3].

Incidence Rate of ALL: Acute lymphoblastic leukemia (ALL) is diagnosed in approximately 2000 children in the United States each year, whereas acute myeloid leukemia (AML) is diagnosed in only about 500 children and chronic myeloid leukemia (CML) in fewer than 100 [2]. Chronic lymphocytic leukemia (CLL), one of the most common leukemias in adults seldom occurs in children. Leukemias and lymphomas followed closely by tumors of central nervous system constitute the vast majority of childhood cancers in India. In different population based cancer registries, leukemias constitute 27% to 52% of childhood cancers in males and 19% to 52% in female. It was estimated that within a population of 882 million, six thousand children would develop acute lymphoblastic leukemia each year in India [4].

About 6,000 cases are reported in the United States every year [5]. Internationally, ALL is more common in Caucasians than in Africans; it is more common in Hispanics and in Latin America [6, 7]. Cure is a realistic goal and is achieved in more than 80% of affected children, although only 20-40% of adults are cured [3]. "Acute" refers to the relatively short time course of the disease, distinguishing it from chronic lymphocytic leukemia, which has a potential time course of many years [8, 9].

Pharmaceutical Approach to Cure ALL: ALL was one of the first cancers for which an effective chemotherapeutic treatment was developed. Antifolates like aminopterin and methotrexate were developed in the late 1940s by Sidney Farber and Yellapragada Subbarow [10, 11].

Pharmaceutical Development to Tackle ALL Form of Leukemia Failed to Keep Pace With the Disease: Since then, despite great progress in the treatment of children and adults with acute lymphoblastic leukemia (ALL), substantial numbers of patients continue to die of this disease and the short and long-term toxicities of standard therapy are substantial [12-14].

Monoclonal Antibodies and ALL: Therapies that rely on action of target specific monoclonal antibodies are considered to be a silver bullet in the war against ALL-form of leukemia. It has the potential to address the issue of chemo-resistance and is associated with far lesser levels of toxicity compared to its chemical counterpart [15]. However, the most exciting progress in this area is in the form of engineered T lymphocytes that identify and recognize MHC non restricted tumor antigens with the assistance of transducing chimeric antigen receptors or CARs.

CARs posses an extracellular binding domain that is sourced from the antigen binding region of an antibody and linked with trans-membrane and signaling motifs to allow the T cells to target a surface antigen which can be otherwise recognized by an antibody. Clinical results at primary stage indicate highly encouraging tumor destroying effects in patients with leukemia,[16-20] although the most perfect form of a CAR in terms of its molecular design still remain an intense subject of research in the present time.

Cell Therapy for Cancer: An emerging field in pharmaceutical development against cancer. Therapy for cancer using live cells is now crossing the bold threshold of clinical activity because data generated from large trials indicate unsurpassed success in controlling leukemia using this mode of treatment [21-27]. Traditionally, all cell based treatments mainly focused on cytolytic T cells that targeted the MHC-restricted antigens. Even though this strategy still remains a very prospective one, its efficiency and potential for application appears to be restricted because of limited affinity of naturally occurring T-cell receptors (TCR) towards the tumor antigens. This disadvantage is further deepened by a molecular event where the cancerous cells down regulate MHC molecules.

Classical Cell Based Therapy Has Serious Limitations: There are some serious limitations associated with standard and classical cell based therapy. One of them is the challenge to target MHC-restricted antigens in childhood cancer and other rare forms of tumors where immunodominant epitopes are not defined for most MHC alleles. For all these reasons, chimeric antigen receptors (CAR), that possess strong cell destroying capability on one hand and ability to expand the effector population in the other along with MHC-unrestricted targeting, are attracting great attention and form a very promising new therapeutic option for childhood cancer.

CAR Engineering: The specificity of a monoclonal antibody and the killer effect of a cytotoxic T cell. Artificial T cell receptors (also known as chimeric T cell receptors, chimeric immuno-receptors, chimeric antigen receptors (CARs) are genetically modified and laboratory-designed receptors, that impart an arbitrary specificity to an immune effector cell. Typically, these genetically modified molecules possess the specificity of a monoclonal antibody and the cytotoxic capability of a T cell. It is formed by transferring coding sequence of the antibodies to those of the T-cells using retroviral vectors. The receptors are termed chimeric because they possess parts from different sources and molecules.

These artificial T cell receptors are presently under investigation as a potent tool for treating cancer using a technology called termed the adoptive cell transfer [28]. For this, T cells are extracted and removed from a patient and genetically altered such that they express receptors specific to the particular form of cancer that the patient is suffering from. These modified T cells that can now identify and destroy the cancer cells, are injected back into the patient after necessary modifications. Presently research is underway to explore the possibility of using engineered T cells from one donor for use in another person who is suffering from the same form of cancer.

Monoclonal antibodies (MAbs), that include trastuzumab (Herceptin) for treating breast cancer, rituximab (MabThera) for B cell lymphomas and ipilimumab (Yervoy) for melanoma, have already been demonstrated to work as wonder drugs against cancer and has revolutionized the domain of cancer immunotherapy [29].

The addition of the therapeutic potential of T cells to travel and navigate to the point of disease, expand in number and remain so following a single dose of administration continues to be a single major advantage over monoclonal antibodies. This phenomenon has been very well proven through isolation, *ex vivo* expansion and adoptive transfer of tumour-infiltrating lymphocytes (TILs) for treating malignant melanoma [30]. Cancer therapies using only T cells has been restricted by absence of the feature of isolation and expansion of high-affinity T cells restricted to tumor associated antigens coupled with the limited *in vivo* expansion.

The recent development and success of developing genetically engineered T cells. It is now possible to express a unique high-affinity T cell receptor (TCR) or a chimeric antigen receptor (CAR), both of which can impart new tumour antigen specificity. It has now been demonstrated that a suitable amount and quantity of genetically engineered T cells may be produced for adoptive transfer into the patient after necessary genetic modification to bring together the specificity of a monoclonal antibody and cytotoxic effect of a T-cell. Such event has already been demonstrated to act satisfactorily against cancer [31-33]. Yet another advantage of T cell therapy compared to conventional therapies is the possibility of precise lysis of antigen-positive cells, leaving other tissues intact and untouched.

CARs: CARs are a combination of antibody-like recognition capability coupled with the activating function of T-cells [34] and mainly composed of three distinct regions as an antigen binding region derived from antibody [35], a trans-membrane domain (TM domain) which facilitates the anchoring of CAR to T-cell [36] and single or multiple intracellular domains imparting effector functions in transduced T-cells [37, 38].

Unlike the physiologic TCRs, CARs even recognize the unprocessed antigens autonomous to expression of major histo-compatibility antigens [39]. They have binding affinity for a wide range of potential targets encompassing not only proteins,

but also ganlioside [40], carbohydrate [41], heavily glycosylated protein [42] and proteoglycan [43]. The presence of single chain variable fragment (scFv) aka the targeting domain formed by self association of heavy and light chains of monoclonal antibody determines the specificity of CARs [44]. The binding of CARs to target molecules is similar in mechanism to antigen-antibody interaction. Factors affecting the CAR-mediated T-cell response are topological structure of epitopes, affinity of scFv and the expression level of antigen on tumor cells [45].

Structural Uniqueness of CAR-T Cells: The accessibility of CAR T-cells to an epitope is determined by the flexible hinge region between the trans-membrane domain of CARS and the targeting moiety. The commonly employed trans-membrane domain is CD3ζTM domain, as it forms homodimers which are incorporated into endogenous TCR complex. The other TM domain which are employed are CD28, CD3z, CD8, CD4, FcRγ, etc [46].

To fulfill their antitumor function, it is important for the CAR T-cells to have a thoroughly designed intracellular signaling domain. The newer generation CARs are designed in such a way that they contain a second signaling domain. These newly added signaling domains are the cytoplasmic domains of co stimulatory receptors such as CD137, CD28, CD134 or inducible co stimulator. The addition of such domains increases the production of cytokines and tumor-lytic activity and decreases the activation-induced cell death [47].

Production of CAR T-Cells: To produce CAR T-cells, firstly T-cells are collected from the patient by a process called apheresis. It is a process by which blood is withdrawn from the body followed by separation of plasma or white blood cells. The remaining components of blood is returned back into the patient's body. The T-cells are than isolated and are transfected with a viral vector such as lentivirus containing the CAR genes directed against a specific antigen. Once the CAR gene-containing virus binds to the T-cell membrane, reverse transcription, DNA integration followed by expression of CAR gene occurs. The CAR genes are than translated into CAR proteins into the cell membrane of the T-cells. The genetically modified T-cells are cultured in the laboratory and subsequently injected in patient followed by monitoring of the response [48].

CONCLUSION: Dramatic scientific achievements has been done in recent times in the domains of genomics [49, 50], cancer biology [51], and immunology [52] in order to have a more effective and less toxic targeted treatment for childhood cancer [53]. CAR-based cell therapies have emerged to be one of the most novel and prospective research outcomes that amalgamate the advantages of genetic engineering and adoptive immunotherapy.

The present attention now is to achieve desired targeting of the tumor cells along with little or minimal toxicity towards normal cells. The other approach is imparting required cell expansion capabilities within the body that can make the therapy more viable and cost effective.

A large number of antigens are already identified for paediatric cancer that can be used as effective target for genetically designed CARs. For cell manufacturing, review show that several approaches can successfully generate large population of CAR but all of them await carefully designed trial experiments to evaluate their true potential as suitable therapeutic molecules for treatment of cancer. The other important aspect is adequate modulation of host factors that hold key to desired *in vivo* expansion and persistence. Due to limited patient numbers in trail studies

Given the limitation in child hood cancer patient numbers that severely restrict adequate early phase trials using genetically modified T cell receptors, it is anticipated that most information would arrive from research undertaken in the domain of adult oncology, or in trials that comprise of both adult and paediatric patients. Ultimately, however, proper and well designed clinical trials would any ways be required to be conducted in children to estimate the efficacy and toxicity of this new modified T cell therapy. Assuming that suitable and desired trial results emerge, we anticipate dramatic surge in efforts for large scale manufacturing of these molecules at commercial scale to reduce cost and make the therapy cost effective.

It may be envisaged that such a treatment will include host preparative regimens and new

elements in the cell expansion formulation to enhance *in vivo* expansion.

Despite the fact that most of the antibody based therapies are most effective in the backdrop of minimal residual disease stage preliminary results show that CAT-T cell therapy can work even when these is significant and large tumour burden in the patient. For trials performed in minimal residual disease setting, novel clinical trial endpoints are required to determine whether results from early-phase trials require larger randomized trials with survival endpoints. Careful assessment is also required to understand the right time for initiating CAR-based adoptive immune-therapies, and to compare this type of therapy with traditional mAb-based immune-therapies.

In summary, the CARs has emerged as a novel and promising technology for targeted therapy of childhood cancer. Dramatic progress in this domain can only be achieved if academia takes charge duly supported by funding such that a new type of targeted immunotherapy for children with cancer is developed.

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