PEER REVIEWED

Precision Medicine: Targeted Therapy in Paediatric Oncology Patients

For several decades, cancer has been one most of the devastating diseases affecting paediatric patients. A huge number of clinical trials and research papers are aimed at solving the puzzle of cancer; however, most scientists and healthcare providers are often shocked by the unpredictable attitude and response of this disease.

Nevertheless, huge progress has been made in this field as about 50 years ago, the 10-year survival rate didn't exceed 20% (patients < 20 years old); but nowadays, it has reached 83%. This has been made possible by the efforts of the cooperative group protocols and multidisciplinary treatment.[1] However, the toxicities and adverse effects exhibited by chemotherapeutic agents remain a barrier while treating paediatric oncology patients. In such circumstances, precision medicine can help us deal with the above issues.[2]

In 2015, Mr Barack Obama, the president of the United States, launched the "Precision Medicine Initiative".[3] Furthermore, he described it as being equivalent to the first moon landing as it aimed at providing individualised care to cancer patients.[1]

What is Targeted Therapy? And What are its Advantages?

Targeted therapy depends on targeting unique receptors or proteins in the malignant cells, thus leading to fewer chemotherapy-induced adverse effects.

In this regard, a study published in the Oncology Times aimed at evaluating the efficacy of targeted therapy in paediatric oncology patients with poor prognosis.[4] The trial included 149 children with relapsed, refractory, and progressive high-risk malignancies (survival rate: less than 20%; median survival: 9.5 months). By using a particular algorithm, the paediatric oncologists could identify twenty patients with very high priority targets who could benefit from targeted therapy. After receiving the appropriate targeted therapies, these children showed longer progression-free survival than other children (204.5 days versus 114 days).

Thus, to achieve the highest benefit from the targeted therapy, we would have to focus on developing the diagnostic tools to facilitate identifying the highest priority targets in each patient.

But although targeted therapy can achieve better results, there are only a few approved targeted therapies available for paediatric oncology patients. Thus, the American Society of Clinical Oncology (ASCO) urges the scientific community to undertake precision medicine research and treatment approaches as a critical research priority. But even as it does so, we must be aware of the various challenges faced while developing and using targeted therapy in the paediatric population.[5]

Challenges of Including Paediatric Population in Clinical Trials

To include paediatric patients in clinical trials is not an easy task. According to the European Society for Medical Oncology (ESMO), the legal age in Europe for participation in clinical trials is above 18 years. However, it's lowered to 12 years in the USA.[6]

Moreover, cancer in paediatric patients has a different histology[3] with a few numbers of mutations and genetic alterations in contrast to adults, and this hinders the development of new targeted therapies.[1]

However, the MATCH-style trials (paediatric cancer clinical trials) are extending its purview to include participants from various countries as Europe (ESMART), Canada (PROFYLE), and United States (NCI Pediatric MATCH).[2] And now, let us focus on particular types of targeted therapies for paediatric oncology patients.

I. Anti-angiogenic Therapy

For nutrient supply to cancerous tissue, new blood vessels originate from the pre-existing ones. This process is known as angiogenesis and is crucial for the growth of the malignant cells.

The VEGF (vascular endothelial growth factor) pathway is pivotal for the process of angiogenesis, so most anti-angiogenic drugs, like Bevacizumzb, Sunitinib, and Cediranib, target the VEGF pathway and receptors.[5] These drugs decrease the tumour's interstitial pressure and increase the oxygen delivery to the tumour while decreasing vascular oedema and enhancing the delivery of chemotherapy at the target site.[7]

In alveolar soft part sarcoma, a rare type of cancer with a prominent capillary vascular pattern, the tumour cells have a poor response to chemotherapeutic agents. But by adding Cediranib and Sunitinib, the tumour cells have shown a good response.

Cilengitide, Pazopanib, and Sorafenib are examples of the other anti-angiogenic agents, which are being examined for various malignancies in paediatrics.

II. Immunotherapy

Although the immune system can defend our bodies from viruses and bacteria, its protective mechanism is weak against cancer cells. Immunotherapy aims at boosting the immune system to target the malignant cells. It is now considered the fifth pillar in cancer treatment, and over 40 ongoing clinical trials are examining the effect of different immunotherapies to treat paediatric cancer patients.[1]

Vaccination

In various paediatric solid tumours (neuroblastoma, hepatoblastoma, high and low-grade glioma, atypical teratoid rhabdoid tumour), the result of vaccination was promising as it increased the survival rates even with high-risk sarcoma.

Monoclonal Antibodies

In 1997, the FDA approved the first monoclonal antibody Rituximab (targets the CD20 antibody) to treat malignant lymphoma. Nowadays, Blinatumomab (targets CD19 and CD3) is approved to treat B-cell acute lymphoblastic leukaemia (ALL) in adults and is used off-label in relapsed B-cell ALL in paediatric oncology patients.

Chimeric Antigen Receptor Transgenic T-cells (CAR T-cells)

The T-cells are extracted from the patient's blood; then, it undergoes

genetic engineering to add the chimeric antigen receptors on its surface (CARs). In this way, T-cells can target particular antigens on the tumour cells' surface once it is injected back into the patient.

The CAR T-cell therapies targeting CD19 in B-cell ALL were commonly used in several clinical trials, and they showed encouraging results. An early clinical trial included 30 patients with ALL (children and young adults), and twenty-seven patients showed complete remission without recurrence signs. Then, large-scale clinical trials were conducted to ensure the efficacy and safety of CAR T-cells.

In August 2017, the FDA approved the release of Tisagenlecleucel for children and adolescents with ALL. However, as some leukaemic cells may become CD19 negative due to antigen loss, several clinical trials were directed to investigate the results of CAR T-cells when targeting CD22. The outcomes of these trials showed promising results as there were complete remissions with no signs of relapse.[8]

III. Tyrosine Kinase Inhibitors

A hallmark event in cancer is the uncontrolled proliferation of cells during suppression of differentiation and cell death. Such an event is facilitated by dysregulated activation of tyrosine kinases (responsible for transmitting signals). Thus identification of dysregulated kinase can form a potential therapeutic target for the treatment of cancer.

In this, the identification of tyrosine kinase inhibitors (TKIs) in adults has paved the way for its use in paediatric oncology patients.[9] The various TKIs available today include Imatinib, Lestaurtinib (FLT3 TK family), Neratinib, and Brigatinib.[10,11] However, most of these drugs are effective only for a short time (except in CML) when used as monotherapy.[9,12]

IV. BRAF and MEK Inhibitors

Genetic mutation is the basis for the pathogenesis of cancer. BRAFV600E is one such genetic mutation that induces activation of the mitogen-activated protein kinase (MAPK) signalling pathway that affects cell proliferation, differentiation, and survival.[13]

Trials with BRAF-mutant xenograft models have shown that suppression of MAPK signalling by BRAF inhibitors results in tumour regression and may prove to be an effective therapeutic option in patients with BRAFV600-mutant cancer types. Therefore the USFDA and EMA had recently approved Vemurafenib and Dabrafenib for the treatment of unresectable or metastatic melanoma with mutant BRAFV600.[13] BRAF mutations are also known to be responsible for paediatric cancer; these genetic aberrations have been identified in the paediatric population with malignant melanoma (50%), gangliogliomas (50%–60%), and high-grade astrocytomas (10%-20%).[14,17]

Thus, BRAF inhibitors form the cornerstone for BRAF mutated malignancies. However, one must also take into account the incidences of drug resistance (BRAF inhibitors), which result in reactivation of the MAPK[18,19] pathway. Here, the use of combined therapy (BRAF and MEK inhibitors) has demonstrated its ability to overcome resistance in a metastatic melanoma cell.[13]

V. Proton Beam Therapy

Precision radiotherapy has been known to deliver the dose on the tumour. It includes intensity-modulated photon radiotherapy (IMRT) and proton beam therapy (PBT). Both of these treatment modalities developed in the late 1990s; however, as time passed, it was proved that PBT had the upper hand over IMRT in terms of dose distribution and dosimetric control. Initially, the use of PBT was limited to tumours near the critical structure, or those that responded poorly to IMRT. Nevertheless, in recent years, PBT has been applied to treat other neoplasms as well.[18] Furthermore, due to the improved sparing characteristic of normal tissue, PBT nowadays is also being used in the paediatric population.[19]

Yet, there are at least three limitations[18] in published data that hinder the large-scale use of PBT. These include:

- Studies are retrospective in nature
- The small sample size of prospective studies
- The lack of head-to-head comparison between the PBT and conventional radiotherapy

Targeted Therapy: The Other Side of the Story

While targeted therapy is traditionally believed to have lesser side-effects than its non-specific counterparts, it has some side-effects:

- TKIs as Imatinib lead to significant growth retardation in children receiving them on a chronic basis for the treatment of CML[20]
- Second- and third-generation BCR/ABL TKIs are linked to vascular adverse events, like pulmonary hypertension and occlusive events[21]
- CD19 CAR T-cell therapy has been evidenced to result in disruption of the blood-brain barrier, leading to neurotoxicity and an increase in the risk of infection (due to depletion of B cells)[22,23]
- Almost 85% of melanoma patients treated with Ipilimumab suffer from autoimmune adverse effects[24]

Moreover, targeted therapies also pose a financial burden on the patient. As of 2018, the costs for Dinutuximab beta was around 173,000€ in the treatment of a paediatric neuroblastoma patient. 1 Similarly, treatment with Tisagenlecleucel (CD19 CAR T-cell therapy) would almost add 330,000$ more to a patient's medical expenditure as compared to traditional chemotherapy for B cell acute leukaemia.[25]

Conclusion

In recent years, the field of precision medicine has experienced some of the most spectacular breakthroughs. However, an increase in the number of prospective trials would facilitate the large-scale use of PBT in paediatric oncology patients. Finally, a continued venture for newer drug development and improved sequencing technique is sure to further expand the scope of precision medicine in paediatric oncology.

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