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Future Frontiers in Paediatric Oncology

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Introduction

Paediatric oncology is the field of medicine relating to the care and treatment of childhood cancers. Over the past two decades, the remission rate has been increasing due to improved treatment methods[1]; however, a number of aggressive forms of malignancy still affect this cohort[2]. These rarer forms of cancer do not respond well to conventional treatment, presenting a significant challenge for paediatric oncologists due to their unique genetic profile and rapid progression. This paper seeks to explore two new frontiers in paediatric cancer treatment: the fields of genetic testing and targeted treatment strategies. Combined, both of these domains not only present a promising approach toward treating childhood cancers through personalised medicine, but also earlier detection leading to improved survival rates.

Epidemiology

The global incidence of childhood cancer is 140-155 million per year in those under 15, and 210 million per year in those aged 15-19[3]. The most common diagnostic groups are leukaemias (34%), brain tumours (23%), and lymphomas (12%)[4]. Childhood cancers are a significant cause of morbidity and mortality, accounting for 23% of deaths in children aged 4-15. Malignant neoplasms have been identified as the second leading cause of death in this age group[3,5]. However, with advances in modern medicine, the survival rate of paediatric cancers is 83%, a large improvement from the 20-30% in the pre-chemotherapy era of the 1960s[3,6].

Genetic Testing

Genetic testing is a rapidly emerging field with applications in a variety of cancer predisposition syndromes (CPS)[7]. CPSs are caused by germline mutations in tumour suppressor genes, growth factors, and DNA repair genes1. Approximately 10-15% of children with cancer will have an underlying CPS[7].

Furthermore, studying patients with a potential CPS is important in the development of discovery of inheritable mutations, cancer screening, treatment, follow-up protocols, and family support[8]. A limitation to the integration of genetic testing into the referral and management of patients with potential CPSs is that of the provider: research has shown that paediatric oncologists do not feel confident regarding the genetic testing procedure, and instead prefer to refer patients to a geneticist[9].

Current tools for genetic analysis include next-generation sequencing, a high-throughput method which allows for quick sequencing of a desired genome that is both sensitive and accurate[10]. The availability of sequencing technology throughout laboratories has widened the spectrum of its use, including research applications, clinical trials, and clinical investigations[11].

Targeted Treatment

The discovery of various CPSs has allowed for the development of targeted therapies for paediatric oncological conditions, increasing the standard of care by removing the need to use chemotherapeutic and radiotherapeutic options and therefore its short- and long-term side effects[12]. Immunotherapy is an effective therapy which aims to target a patient's individual mutation with antibodies to nullify its function[13], thus reducing toxicity compared to conventional methods[14]. Current practice utilises immunotherapies such as blinatumomab and chimeric antigen receptor T-cells (targeting CD19 and C22 respectively) for refractory B-cell precursor acute lymphocytic leukaemia[14].

In recent years, Clustered Regularly

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Interspaced Short Palindromic Repeats (CRISPR) therapy has developed as a potential targeted therapy method. CRISPR systems exist naturally in a broad array of bacterial species, which work to splice DNA at specific locations and sequences in order to allow for genome editing[15]. Tangible clinical applications of CRISPR include diagnosis by recognition of microsatellite mutations, which are diagnostic markers in particular cancers[15]. Furthermore, ex-vivo CRISPR therapy would involve engineering T-cells to attack a particular target, a method currently being used in research applications to date[15]. The ideal goal would be to effect in-vivo cell change using CRISPR, allowing for direct tumour cell therapy and disruption of the tumour promoting gene within[15]. However, there are multiple variables that limit the applicability of CRISPR as a clinical therapy in the current moment, including proper delivery of the CRISPR machinery directly to the tumour cells, and the researcher's ability to artificially edit a cell genome within a cell that naturally resists editing[15].

Ethical Considerations of Paediatric Oncology Research

The implementation of genetic testing and targeted treatments into the clinical environment is not without significant challenges. The ethics of cancer care is a broad and complex aspect of oncology which is further compounded when it pertains to the care of children. Research into the treatment of cancers often deals with the care of individuals who are vulnerable due to the emotional and physical limitations placed on the person by the diagnosis. Thus, conducting research into novel treatments on this cohort must ensure the patient is fully aware and consents to participation. This leads to an overlap of two fields with fundamentally different aims: patient treatment and cancer research. Patient treatment places an emphasis on the care and survival of the patient, with minimal consideration for developing new knowledge[16,17]. In contrast, cancer research prioritises the pursuit of knowledge and solutions, with less regard for the therapeutic benefits[16,17]. This overlap is a grey area which is hard to reconcile, particularly when weighing against the emotional care of the child and parents.

To confront this, paediatric physicians and nurses have identified three key areas of consideration: (1) positive communication with the patients and their family, (2) acknowledging the vulnerability of the patient, and (3) balancing the best interest of the patient and their parents in their respective roles in a parent/child relationship[18]. Such considerations can allow for the safe integration of both patient care and cancer research within paediatric oncology, developing a mutually beneficial approach for the child and their family.

Conclusion

Ultimately, personalised medicine such as genetic testing can aid therapeutics in paediatrics by providing an avenue for targeted treatments. Genetic testing could identify childhood CPS, with direct clinical therapeutic applications. Technologies such as CRISPR and immunotherapies can alter current practices to reduce current regime toxicities. However, ethical considerations in balancing patient treatment and advancements in cancer research play a major role in the implementation of novel therapies. An understanding of genetic testing and targeted treatments could create a nuanced therapeutic regime in paediatric oncological patients that centres around each child as an individual.

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