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Analysing Nanotechnology in the Paediatrics Medicinal science with reference to the Central Nervous System

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ABSTRACT

Nanotechnology has been an impeccable scientific tool to address and overcome pharmaceutical and biological drawbacks such as poor aqueous solubility, low physicochemical stability and insufficient bioavailability. Because conventionally the development of paediatric treatments usually relied on the previous experience in adults and the clinical testing being carried out in an aged environment, there do not exist approved paediatric nanomedicines yet. While various chemotherapeutic agents can be utilized to improve the survival rate of patients with ovarian cancer, their distribution throughout the entire body results in high normal organ toxicity. Further, all the existent treatments for paediatric science pertaining to the Central nervous system are either of less efficiency or comprise of higher level of cellular Cytotoxicity. This short review deals with the two common tumours of the central nervous system occurring in children and the current scientific advances applied on it with respect to nanotechnology. In addition, we have discussed on the benefits of using nanotechnology to address the complications in the central nervous system because of its small size (10-100 nm) of particles which improves circulation and enables superior accumulation of the therapeutic drugs at the tumour sites, especially in infants.

KEYWORDS- Nanotechnology, Paediatrics, Medulloblastoma, Astrocytoma

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1. INTRODUCTION

There exist several researches which demonstrated that children have a very different capacity and a pathway for drug absorption. Several theories claim perhaps it is because of their bio distribution, metabolism and excretion with respect to adults¹. Furthermore, several pharmacokinetic studies have showed that the dynamics and the environment in which a drug acts on a child's body is completely different from that of an adult due to the direct adjustment of the dose to the body weight/surface ratio. If the paediatric population is divided into five groups namely newborn infants (0–27 days), infants and toddlers (28 days–23 months), preschool children (2–5 years), school children (6–11 years) and adolescents (12–16/18 years), we will see that each group exhibits different level of intestinal mobility, drug conjugation and delivery system along with pH transition. In case of inhalatory products, the cognitive development can also effect the drug formulation and the possible clinical trials²⁻⁵. The toxicology aspect with respect to the nanoparticle used in the drug should be thoroughly tested because children show a higher response to the particle deposition. A very famous citing example is that several nano DDS comprising of the biocompatibility liposomes have reached clinical phase in case of adults but it is still restricted to trials in children. This short review is aimed to focus on the tumours of the central nervous system using nanoscience as a solution, keeping paediatric science on the backdrop.

2. ANALYSING THE TUMOURS OF THE CENTRAL NERVOUS SYSTEM

2.1 MEDULLOBLASTOMA

As far as the Central nervous System is concerned, Medulloblastoma is one of the major malignant paediatric neoplasms. It is a very aggressive and invasive primary brain tumour localized in the cerebellum and the posterior fossa with a high tendency to metastasize⁶. Lu et al had carried out a survey which resulted that the incidence of this particular disease is approximately 9.6 cases per million children and the current survival rate is 65%. Although the figures have improved from a drastic 30% to 65% in 2015, the science is still striving more every day to improve the survival rate. It is worth noting that Medulloblastoma in children and adults are genetically and histologically different and they have been recently classified into four well defined molecular groups. The challenge lies in the fact of identifying the correct phasic disease and proposing the proper therapy for the same, which implies to the importance of the paediatric clinical trials⁷. The cellular and molecular mechanisms that generated, maintain and overlap the progression of Medulloblastoma remain constant though the Hedgehog signalling pathway has been related to the development of one type of the disease.

Drugs such as vismodegib had been proposed by various scientists which is currently under clinical trials in adults and this could eventually expand the therapeutic drug design in children. Other cellular targeted drugs based on microRNA have been a prime focus for the scientists because of its high repository effect. These short non-coding RNA sequences (22 nucleotides) regulate transcriptional and post-transcriptional stages of gene expressions⁸⁻⁹.

Keeping these of the pharmacokinetic potential of these molecular targets, the first investigations at the overlaying areas of Medulloblastoma and nanotechnology employed commercially available liposomal formulations approved for the treatment of adult tumours. A major reason for the above assertion was that since patients, especially adults enter into several sub classes of Medulloblastoma was found to be the best suited for clinical trials from both a regulatory and an ethical perspective. Boiardi et al. studied the safety and functionalization of daunorubicin-loaded liposomes in adult patients with advanced recurrent gliomas and Medulloblastoma. The results pertaining to Medulloblastoma turned out were positive¹⁰. Piccaluga in the early 2000 synthesised a drug framed on the similar composition with added agents (DuanoXome®) for the clinical evaluation in relapsed meningeal acute myeloid leukaemia. The reports suggested that since liposomes overcome the blood brain barrier system; they can be a potent treatment agent for the tumours of the Central Nervous System. Since then, only countable preliminary studies explored nanotechnology platforms to improve the therapy of Medulloblastoma¹¹⁻¹⁵.

Zucker and Barenholz recently fabricated a matrixed liposomal combination of vincristine and topotecan co-encapsulated in the same nanocarriers to simultaneously deliver them to human Medulloblastoma cell line with positive results. Although the studies of the same in vivo model are pending, scientists are striving hard to develop an alternative drug delivering strategy highlighting paediatrics. Lim and co-workers developed curcumin-loaded nanoparticle made of N-isopropylacrylamide, vinylpyrrolidone and acrylic acid (NanoCurc®) and demonstrated a dose-dependent decrease in the growth of Daoy and D283Med cell lines in vitro especially when subjected to an infant's body. The most interesting contribution of this project was that the changes in the CD-133 characterised stem like spherical projections were turned out to be synchronous with the clinical trials of children¹⁶. Moreover, the gene regulated expression of IGF-1, STAT3 and GIL1 which are majorly responsible for the growth of Medulloblastoma showed depreciation when subjected to the nano curcumin.

The relevance of in vitro assays should not be overestimated, especially because this type of cancer is characterized by the fast dissemination and the invasiveness of its cells in different areas of the CNS and the conservation of an intact blood-brain barrier.

It is generally difficult to create the analogous human environment especially in intermitted stages on infancy to measure the exact efficacy of the system¹⁷. Meng et al had developed the in vitro model of the brain tumour in these exact environments. The next challenge, after this would be the development of an appropriate xenograft model to study the pharmacokinetics within a children system response.

The last semi decade had seen the emergent of theranostics which is a blend of therapeutics and diagnostics as a new concept to address the problem of this disease treatment. Sun et al. used super paramagnetic nanoparticles comprising of Fe₂O₃ surface-modified with PEG and chlorotoxin, a peptide isolated from scorpion venom that shows great affinity for neuroectodermic cells, to deliver an antitumoral drug (methotrexate) and an MRI agent to Medulloblastoma (D283) and glioma (9L/lacZ) cell lines and to murine xenograft glioma model simultaneously. The same ligand was used to target a nano-vector/DNA complex to Daoy cells¹⁸⁻¹⁹.

2.2. ASTROCYTOMA

Astrocytoma is another class of intracranial brain tumours similar to that of Medulloblastoma originated in glial cells called astrocytes. It can develop in any zone of the brain and also in the spine spacing the risk for the disease to spread throughout the entire Central nervous system very quickly²⁰. Based on the recognition of anaplasia (nuclear atypia, cell pleomorphism, mitotic activity, endothelial hyperplasia and necrosis) and histological analysis, the WHO classifies astrocytomas according to growing malignancy into grades I (polycystic and subependymal giant cell astrocytomas), II (pilocytic, pleomorphic xanthoastrocytomas and Diffuse astrocytomas), III (anaplastic astrocytoma) and IV (glioblastoma multiforme).

Lower grades of astrocytomas are considered to be the benign tumours having the highest occurrence rate amongst the infants. The present prognosis is good, though it depends on the brain mass lost after surgical resection. Since, these tumours are quite heterogeneous in nature; the improvement pathway is quite complicated as they could be effective in one type and ineffective in the other²⁰.

This also challenges the conduction of clinical trials which might have an impeccable role in the paediatric science. Only a few preliminary studies addressed the use of nanotechnology to treat this type of cancer, most of them focusing on high grade astrocytomas that are more characteristic of the adult population. The most common nanocarriers was PEGylated and ligand-conjugated liposomes, most often loaded with camptothecin, limesin or doxorubicin²¹⁻²².

3. CONCLUSIONS

The nanoscience has taken a prospective route to address the Tumours of the central nervous system from the past decade. The Australian Centre for Nanomedicine at the University of New South Wales (Sydney, Australia) had carried out a research which showed that the fate of pediatric nanomedicine seems to be intimately linked to the progresses made in the implementation of these innovative therapies in adults, which is further constrained by the absence of a rigid framework of regulation. In other words, from an ethical perspective, the support of the implementation of the “Precautionary principle” what would make the implementation of nanotechnology in children a possibility only in the long-term range and after very extensive and meticulous research. In the same way, diseases which have a less survival factor in case of children should receive a special attention to assure better medical treatment²³. The most effective and the primary responses should be to be the foundation of research clusters in academia and industry that address, in a focused and multidisciplinary way, the treatment of each single disease at the paediatric level. Otherwise, the current adult–child gap is expected to undergo a further deepening and the paediatric patients left one more time behind.

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