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Short Communication

Current Trends and Future prospects for Neuroblastoma Therapeutics

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Abstract

Neuroblastoma (NB) is the most common cancer diagnosed in infants and the most common extra-cranial solid tumor in children. The clinical course of the disease is highly variable with frequent spontaneous regressions observed in patients less than 1 year of age, while it presents with a much higher risk of a poor prognosis in older pediatric patients. Due to the heterogeneous presentation of NB, stratification of patients via numerous diagnostic procedures, and subsequent appropriate treatment strategies conforming to the varying stages of aggressiveness of the disease have been developed.

Design and execution and evaluation of the findings of clinical studies involving NB patients have been performed largely by a select groups of experts leading to substantially deeper knowledge of the pathophysiological mechanism(s) and the diagnosis of NB while still leaving a lot more effort to be expanded for substantially improving the prognoses for patients, especially those with medium and high risk disease.

Several exhaustive reviews are currently available on NB therapeutics including accounts of clinical trials. This brief overview intends to examine only some of the currently available treatment strategies, regarding their respective therapeutic efficacies, including a focus on long and short term toxic off target effects. A brief assessment of potential opportunities, with a special emphasis on nanotherapeutics, for achieving improved outcomes for NB patients is also included.

INTRODUCTION

Neuroblastoma (NB) is the most common cancer diagnosed in infants and the most common extra-cranial solid tumor in children [1]. The clinical course of the disease is highly variable with frequent spontaneous regressions observed in patients less than 1 year of age, while it presents with a much higher risk of a poor prognosis in patients older than 18 months of age [2]. Due to the heterogeneous presentation of NB, stratification of patients via numerous diagnostic procedures, and subsequent appropriate treatment strategies conforming to the varying stages of aggressiveness of the disease have been developed [3].

Evaluation of the findings of clinical studies, conducted with NB patients, have been performed largely by a select groups of experts [4,5] leading to substantially deeper knowledge of the pathophysiological mechanism(s) and the diagnosis of NB while still leaving a lot more effort to be expanded toward achieving substantially improving the prognoses for patients, especially those with medium and high risk disease.

This brief review intends to provide an overview of some of the currently available treatment strategies, regarding their respective therapeutic efficacies, in addition to assessing potential opportunities for achieving more effective therapeutics with improved patient outcomes.

DISCUSSION

Overview of selected, currently available treatments

Surgery: Surgery is used to treat especially high risk (Grade IV) advanced neuroblastoma with some success. The benefits for patients derived from the extent of the resection is somewhat controversial [6,7] although it has been endorsed by more recent studies as beneficial, based on the findings of other research groups [8-10].

Chemotherapy, stem cell rescue and myeloablation therapy: The use of these approved but still potentially dangerous therapeutic approaches for high risk neuroblastoma (HRNB), while supplanted total body irradiation, induced highly undesirable side effects, including hearing loss, orthopedic, renal and neuropsychological impairment [11]. Another study by Elzembely et al. [11], reported a similar array of late side effects, including hearing loss, growth failure, hypothyroidism, hypogonadism and secondary neoplasms, subsequent to the conclusion of intensive induction chemotherapy, followed by myeloablative consolidation chemotherapy and triple autologous stem cell transplants [12].

Even more serious concerns were raised regarding post-treatment side effects occurring in countries with limited resources. Specifically, sinusoidal obstruction syndrome

occured following busulfan/melphalan therapy resulting in 50% mortality among those affected. In addition "moderately severe" hepatitis was observed in other patients undergoing therapy. The authors concluded that high-dose chemotherapy with autologous stem-cell rescue was feasible in a country with limited resources (e.g. Egypt), where busulfan/melphalan therapies is preferred due to fewer infections, and lower incidence of nephrotoxicity. In this study [13], hepatic complications were also considered to represent a major concern.

Facilitation of chemotherapy via nanotechnology: Nanoparticles, so far, have been studied only to a limited extent in studies involving pediatric cancers [14], including, drug delivery using synthetic lipoproteins [15] and clustered nanostructures [16] to delivered drugs NB cells or to cells from patient derived tumors [17].This is somewhat puzzling as pediatric cancer patients could potentially benefit from the protective effects of nanoparticles[17] and thus reducing the toxicity of otherwise harsh treatments [11-13]. We have earlier suggested applications of nanotherapy for pediatric leukemia patients, specifically using reconstituted high density lipoprotein nanoparticles that target the SR-B1 receptor [18] because of the opportunity to reduce harmful side effects. This approach appeared to be highly effective in early pre-clinical studies, resulting in an over 50 fold improvement in the therapeutic index of fenretinide over the free fenretinide [15].

^{131}I-meta-iodobenzylguanidine (MIBG): While the imaging of NB tumors via the radiopharmaceutical ^{131}I-MIBG used with refractory and relapsed NB patients has been established to have diagnostic value toward enhanced tumor imaging [19], Wilson et al. [20], concluded that "^{131}I-MIBG is an active treatment for neuroblastoma, but its place in the management of neuroblastoma remains unclear even though the process has been in use for several decades [21]. The administration of ^{131}I-MIBG requires high initial construction costs for patient isolation, extensive safety precautions [22] and monitoring for hemotoxicity [23]. In order to improve the theranostic efficacy of ^{131}I-MIBG its infusion has been combined with radio-sensitizers [21] and other therapeutic agents, including vincristine and irinotecan or vorinostat [24]. In addition, ^{131}I-MIBG therapy was evaluated as a component of a consolidation regimen in combination with myeloablative chemotherapy and autologous stem cell transplantation [25].

Although the therapeutic outcomes using ^{131}I-MIBG have shown improvements, when combined with other therapeutic approaches [24,25] the side effect profiles of some of these combination regimens were alarming [11,26]. A recent comprehensive study [26] examined the health status of 5987 NB survivors and reported secondary malignancies occurring, especially among patients who underwentintensive multi-modality treatment. The incidence of second malignant neoplasms (SMNs) was remarkably higher in the patient group receiving "high–risk multi-modal therapy" compared to other survivors having undergone surgery or intermediate risk chemotherapy [26].

Immunotherapy: A comprehensive review of recent developments has been provided by Applebaum et al. [21], documenting the multitude of new therapeutic opportunities for managing NB cases via exciting new approaches in immune-oncology. These include GD2 targeted immunotherapy, CAR-T cells, natural killer (NK) cells, checkpoint inhibitors and tumor vaccines. There is a flurry of at least 10 ongoing clinical trials being conducted in this area, surprisingly, the largest number (4) with NK cell related formulations [21].

Because immune-oncology is still in its infancy, the exciting early findings, hailing the arrival of a potential magic bullet in cancer therapy [27], tended to overshadow the reports on resistance to therapy [28] and its accompanying side effects [29]. The ongoing and subsequent clinical trials should provide an objective view of the extent to which immunotherapy will impact the landscape of NB treatment strategies.

CONCLUSION

Because of the advanced stage of the disease (often metastatic and resistant lesions), stage 3 and 4 NB represent some of the most difficult solid tumors to treat. Despite the intensive research and clinical trials conducted, progress toward a cure of this disease has been slow and currently falls considerably short of the mark. Perhaps equally importantly, the complex multi-modal therapeutic strategies resulted in high toxicity and enhanced development of secondary malignancies, up to 15 years, subsequent to treatment [26]. New treatment strategies are thus urgently needed to improve the prognosis for patients with the high risk and relapsed forms of this disease.

Even though nanotechnology is beginning to appear as a useful adjunct even to immunotherapy [30], it is underrepresented in pediatric oncology [14], including in the treatment of NB. Perhaps a stronger focus [31] and enhanced support of research on nanoparticles for NB theranostics, will accelerate the progress toward the barriers that prevent the rapid development of effective therapeutics for this difficult to treat disease.

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