High-Risk Neuroblastoma: Current and Future Therapeutic Strategies

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Abstract

High-risk neuroblastoma remains a significant treatment challenge. Currently, less than half of patients survive, despite intensive multi-agent, multimodal therapies. We give an overview of the current treatment strategy and summarize the evidence for this approach, before discussing options for treatment of refractory and relapsed disease. Finally, we discuss significant international collaborative efforts to improve treatment by specifically targeting the key genetic drivers of neuroblastoma to positively impact on survival.

ABBREVIATIONS


INTRODUCTION

Neuroblastoma is an embryonal malignancy arising from the neural crest and is the most frequently diagnosed extra-cranial solid tumor of childhood. Most children have high-risk disease at presentation, defined by evidence of metastatic spread or amplification of the MYCN oncogene [1]. The treatment of high-risk neuroblastoma has changed extensively over recent decades, but despite intensification of therapy, the outcome for children with this disease remains poor [2].

Chromosomal copy number alterations are frequent in neuroblastoma: MYCN gene amplification is the most common genetic alteration, described in about 25% cases [1]. The most frequent single gene, point mutations seen in neuroblastoma are activating mutations in the Anaplastic Lymphoma Kinase (ALK) gene, which occur in 8-9% of cases [3,4]. ALK mutations co-segregate with MYCN amplification [5] but are also independently associated with poor survival [4].

We summarize the current treatment strategy for high-risk neuroblastoma and the therapeutic options at the time of relapse, or for disease refractory to standard treatment. Finally, we summarize pre-clinical research, focusing on the current most promising therapeutic strategies for neuroblastoma: immunotherapy and the molecular targeting of MYCN and ALK.

Current Treatment Strategies

The protocols outlining the treatment schedules for newly diagnosed children with neuroblastoma are run by a number of co-operative national and international groups such as the Children’s Oncology Group (COG), the International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) and the German Society for Paediatric Oncology and Haematology (GPOH). Although there are differences between protocols, in common are the main structures incorporating induction chemotherapy, surgery, myeloablative chemotherapy with autologous stem cell transplant (ASCT), radiotherapy and minimal residual disease (MRD) therapy (Figure 1).

Induction Chemotherapy

Induction chemotherapy in recent COG protocols is based on the N7 protocol [6] (21-day cycles of cyclophosphamide, doxorubicin and vincristine or cisplatin and etoposide). Results of a recent COG trial (NCT00070200) with the addition of topotecan and cyclophosphamide to the induction regimen are currently awaited [7].

In Europe, a randomized study of a conventional 21 day regimen of alternating cycles of vincristine [0], cisplatin [P],
etoposide [E], cyclophosphamide [C] (OPEC) and vincristine, carboplatin [I], etoposide, cyclophosphamide (OJEC), with an intensive multi-agent chemotherapy regimen using the same drugs delivered at 10 day intervals regardless of hematological recovery, known as rapid COJEC [8] showed an improved 5 year EFS in the rapid COJEC arm, hence this regimen is now standard of care. There is currently an upfront randomization comparing rapid COJEC chemotherapy with modified N7 induction chemotherapy in the SIOPEN high-risk neuroblastoma trial [9].

Local Therapy: Surgery and Radiotherapy
Following an adequate metastatic response to induction chemotherapy, standard practice is to proceed to surgical resection of the primary tumor. In patients with metastatic disease at diagnosis, complete macroscopic resection of the primary tumor has been shown to confer a survival advantage [10-12]. External beam radiotherapy is routinely given after completion of induction chemotherapy, surgery and myeloablative chemotherapy/ASCT and improves local control rates [13,14].

High Dose Chemotherapy
In patients with high-risk disease, myeloablative therapy with ASCT confers an improved event free survival [15]. Recent COG studies have standardly used carboplatin/etoposide/melphalan (CEM) as myeloablative therapy [16] and an ongoing COG study is randomizing the addition of a tandem myeloablative regimen of thiotepa and cyclophosphamide following CEM [17].

Results from the SIOPEN high-risk neuroblastoma 1 trial have shown significantly higher event free survival (EFS) in patients receiving Busulphan/melphalan (BuMel) as myeloablative therapy compared with CEM [18]. Preliminary data suggests that BuMel is feasible and tolerable following a COG style induction regimen [19] and this is being further evaluated in both a pilot COG study (NCT01798004) [20] and the current SIOPEN high-risk neuroblastoma trial [9].

MRD Therapy
The differentiation agent 13-cis-retinoic acid is used in the setting of MRD. Although there are conflicting data regarding its efficacy [21,22] this may be explained at least in part by pharmacokinetic studies [23].

GD2 is a disialoganglioside uniformly expressed in neuroblastoma cells [24] but with very limited expression in normal human tissues. Recently anti-GD2 immunotherapy using the Ch14.18 antibody has been incorporated into treatment protocols in the MRD setting. In a COG trial, at 2 years, a 20% increase in EFS has been demonstrated in patients randomized to receive anti GD2 antibody in combination with GM-CSF and interleukin 2 (IL-2), compared with patients receiving 13-cis-retinoic acid alone [25], although an increasing number of late relapses have been seen in the treatment group after completion of 4 years of follow up [26].

Within the SIOPEN HR-NBL trial, a randomization of anti GD-2 antibody +/- IL-2 has reported a significantly higher toxicity burden in the IL-2 group resulting in a number of patients discontinuing treatment early [27], the outcome data for this randomization is awaited. However, an evaluation of long term continuous infusion of anti-GD2 in combination with IL-2 by SIOPEN and German collaborative groups has demonstrated efficacy in relapsed/refractory patients in addition to reduced anti - GD2 related toxicity [28].

Relapse and Resistant Disease
10 year overall survival following relapse or progression of high-risk neuroblastoma is extremely poor at ≤2% [29]. Furthermore, a poor metastatic response to standard induction chemotherapy is associated with worse outcome [30]. In a phase II study of patients with an inadequate metastatic response to standard induction chemotherapy, with a combination of topotecan, vincristine and doxorubicin (TVD), 64% of patients had a partial response (PR) or complete response (CR) [31]. This regimen is now used routinely on the SIOPEN high-risk neuroblastoma trial for this group of patients [9].

For patients with relapsed or refractory disease, phase II trials have demonstrated objective responses to temozolomide
although it remains unclear whether addition of irinotecan is beneficial [32-35]. Response rates (CR and PR) of greater than 20% have also been demonstrated with various regimens using topotecan as a backbone in combination with temozolomide [36] or cyclophosphamide and/or etoposide [37-39]. The current Beacon phase II b trial [40] uses temozolomide as backbone chemotherapy with randomized addition of irinotecan and/or bevacizumab (NCT02308527). This adaptive ‘drop the loser’ trial design will next randomize the addition of topotecan to the regimen in view of maturing data from a phase II trial of temozolomide/topotecan showing a 1 year progression free survival of 42% in relapsed/refractory patients [41].

Meta-iodobenzylguanidine (mIBG) is a noradrenaline analogue that is actively taken up by neuroblastoma cells by the epinephrine transporter. When labeled with radioactive iodine-123, mIBG can be used for imaging, and when labeled with iodine-131 it can be used as a targeted radiopharmaceutical. 131I-mIBG is an effective therapy for patients with relapsed and refractory disease that has been used for over 20 years [42-46]. Although 131I-mIBG is beginning to be incorporated into a more frontline setting, to date there have been no randomized controlled comparisons of 131I-mIBG with other therapies [47].

FUTURE PROSPECTS

In addition to these standard chemotherapeutic and radiopharmaceutical options a number of collaborative groups are conducting early phase trials of novel therapeutic agents in addition to novel combinations of established agents. These include the U.S. based New Approaches to Neuroblastoma Consortium (NANT) and the European Innovative Therapies for Children with Cancer (ITCC).

Examples of trials of novel therapeutic agents currently recruiting patients with relapsed/refractory neuroblastoma include a phase I study of the ALK inhibitor ceritinib [48]. As a tyrosine kinase, targeting of ALK holds great potential for the treatment of children with neuroblastoma, however the most common ALK mutation found in sporadic cases of neuroblastoma, F1174L, defines resistance to clinically available ALK inhibitors crizotinib and ceritinib [49,50]. It is likely that for ALK inhibition to be successful, future approaches will require ALK targeted agents to be combined with other small molecule inhibitors. Transgenic models of ALK mutated neuroblastoma provide a valuable preclinical tool for prediction of efficacy of new agents [51-53]. A preclinical study of crizotinib in the transgenic model of high-risk neuroblastoma, Th-ALK(2174E/MYCN), found that whilst ALK inhibition with crizotinib or mTORC inhibition alone was unsuccessful in improving animal survival, a combination of the two compounds resulted in a significantly increased survival with evidence of tumor regression [51]. This combination is now being pursued clinically through the ITCC.

Amplification of the MYCN gene is a poor prognostic marker for high-risk neuroblastoma and efforts to target the expression of MYCN both directly and indirectly appear promising in the preclinical setting [54]. Drugs that target the stabilization of MYCN protein have advanced to clinical studies in pediatrics and a combination of temozolomide and irinotecan with the aurora kinase inhibitor MLN8237 [55] (which is hypothesized to result in MYCN protein breakdown [56]) is underway (NCT01601535).

Immunotherapy also holds great promise for development of effective new therapies. Antibodies against the PD-1 (Programmed Cell Death Protein 1, or CD279/CD274), have been found to enhance the anti-tumor activity of T-cells [56]. A further study of anti-GD2 T-cells in relapsed or refractory neuroblastoma will incorporate a new approach to enhance the longevity of the re-infused GD2 T-cells, whilst concomitantly administering an anti-PD-1 antibody (NCT01822652). In addition there is strong pre-clinical evidence for efficacy of anti-CTLA-4 in neuroblastoma models [57] and a pediatric phase I trial has recently been completed [58].

Substantive preclinical developments will also enable other potentially effective compounds to be transitioned into the clinic. An example of this is the recent description of a high frequency of RAS-MAPK pathway mutations at the time of relapse of neuroblastoma identifying the need for prioritization of clinical testing of MEK inhibitors in relapsed/refractory patients [59]. Furthermore, recent publications sequencing paired tumors from diagnosis and relapse are demonstrating the importance of clonal evolution in neuroblastoma, with sub-clones present at very low frequencies at diagnosis becoming the predominant clone at the time of relapse [60,61]. This highlights the importance of repeat biopsy at relapse for molecular characterization, in order to develop personalized therapy strategies. High throughput molecular analysis of tumors at relapse is feasible and identifies potentially actionable mutations. However limited access to targeted agents for pediatric clinical trials remains a significant challenge[62].

CONCLUSION

In summary, the current treatment protocols for children with high-risk neuroblastoma are complex and continuously evolving. Concerted efforts from groups around the world are contributing to ensure that pediatric patients benefit from novel therapies with the highest efficacy to treat and ultimately cure neuroblastoma. It is only with this continuing cooperation that we will find the most effective therapies to change the outlook for children with this devastating disease.

REFERENCES

6. Cheung NK, Kushner BH, LaQuaglia M, Kramer K, Gollamudi S, Heller...

7. Induction chemotherapy using cyclophosphamide and topotecan in treating patients who are undergoing autologous peripheral stem cell transplantation for newly diagnosed or progressive neuroblastoma. 2014.


9. High Risk Neuroblastoma Study 1.7 of SIOP-Europe (SIOPEN).


17. Comparing two different myeloablative therapies in treating young patients who are undergoing a stem cell transplant for high risk neuroblastoma. 2015.


55. Dubois SG. Phase I/II study of MLN8237 in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma.


