Verschlimmbesserung: Craniospinal Radiotherapy is Essential in WNT Medulloblastoma Patients

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Disclosure: The authors have no conflicts of interest.

Running title: Verschlimmbesserung in WNT Medulloblastoma

Funding: This work was supported by Stan Perron Charitable Foundation (Stan Perron Charitable Trust; to N.G. Gottardo) and American Lebanese Syrian Associated Charities (ALSAC; to A. Gajjar).

Summary
Standard-risk WNT medulloblastoma patients have an excellent prognosis (>90% progression free survival) using the combination of standard dose craniospinal radiotherapy (CSI) (23.4Gy) followed by platinum and alkylator based chemotherapy. A recent pilot study which attempted to completely omit radiotherapy was terminated early as all patients (n=3) relapsed rapidly (on treatment or within 6 months of completing treatment). The study highlights that therapy is the most important prognostic factor, with CSI still required to cure even the most favorable subgroup of medulloblastoma patients.

In this issue of *Clinical Cancer Research*, Cohen and colleagues (1) present the outcome of a prospective pilot study that eliminated the use of craniospinal irradiation (CSI) in the treatment of WNT medulloblastoma. The study was closed to accrual early due to early (3- and 6-months following completion of therapy) recurrent disease in the first two patients. Of the six patients enrolled on the study five patients received irradiation at the time of relapse (n=3) or at the end of planned chemotherapy (n=2). Parents of the last patient opted for high dose chemotherapy with stem cell rescue.

However, the patient developed myelodysplastic syndrome and needed a haploidentical allogenic transplant. Another study that attempted to treat non metastatic WNT medulloblastoma with just focal irradiation therapy and adjuvant chemotherapy also had to be closed early due to recurrent disease in the neuraxis (2). The patients were salvaged by administering high dose (36Gy) CSI, but this salvage strategy defeated the purpose of reduction in long term toxicity in this population.

Using advanced molecular techniques medulloblastoma is defined as a disease that is composed of four distinct molecular diseases, Wingless (WNT), Sonic Hedgehog (SHH), Group 3 and Group 4, each with distinct cell of origin, molecular features, and clinical outcomes. WNT medulloblastoma stood out as a subgroup that occurred in approximately 15% of all newly diagnosed patients (3). Distinctive clinical and molecular features in this subgroup include a median age of 10.4 years, female preponderance (F:M ratio – 2:1); classic histology, presence of monosomy 6, nuclear β catenin on immunohistochemistry and mutations in the *CTNNB1* gene, which encodes for β catenin. These molecular features facilitate identification of these tumors in a timely manner for prospective clinical trials. After the initial reports from prospective clinical trials that have reported an excellent outcome (4, 5), subsequent clinical trials have confirmed the excellent outcome for WNT medulloblastoma treated with surgery, CSI and adjuvant chemotherapy (6, 7).

However, cure often comes at a cost with medulloblastoma survivors often having neurocognitive sequelae that impedes higher education, social functioning, and financial independence (8, 9). Hence, investigators have attempted to modify curative therapy to maintain cure and reduce late effects. Initial studies reported curing medulloblastoma with 36 Gy CSI alone. Subsequent studies reduced the dose of CSI to 23.4 Gy with the addition of adjuvant chemotherapy for patients that had the primary tumor gross totally resected or < 1.5 cm^2 and no metastatic disease (defined as standard risk medulloblastoma), without affecting efficacy (10). However, a recent study that randomized standard risk medulloblastoma patients 3 to 7 years of age between 23.4 Gy and 18 Gy CSI, demonstrated inferior outcome for the latter cohort of patients (7), highlighting the importance of CSI dose in curing medulloblastoma. In this study the randomization did not account for the molecular subgrouping of medulloblastoma and only seven WNT medulloblastoma patients were randomized to receive 18 Gy CSI. This study revealed no statistically significant difference in survival was observed between this group and those patients that received 23.4Gy CSI (7).

Building on the excellent results for WNT medulloblastoma treated with 23.4 Gy and adjuvant chemotherapy three prospective trials are testing disease control with 18 Gy CSI (International Society of Paediatric Oncology SIOP-PNET 5 (NCT02066220); Children's Oncology Group, ACNS 1422 (NCT02724579) and 15 Gy CSI (St Jude Children's Research Hospital SJMB12 – (NCT01878617) and adjuvant chemotherapy (Table 1). These studies have completed or are close to finishing accrual and the results are eagerly awaited. Though investigators focus on reduction of CSI dose to reduce long term sequalae of therapy there have been several refinements in therapy that have led to reduction of toxicity. Proton beam therapy is getting more accessible across the globe and early reports document lesser impact on CNS toxicity as compared to photon beam therapy (11). Reduction of the radiation boost dose from the entire posterior fossa to a 0.5 mm margin surrounding the tumor bed has spared the

temporal lobes and cochlea from additional radiation exposure. Delivery of radiation therapy using parallel opposed fields to sophisticated 3-dimensional conformal radiation therapy or intensity modulated radiation therapy (IMRT) has spared radiation to critical structures of the brain. Improvements in surgical technique has facilitated safe resection of the tumor and optimized MRI imaging has facilitated accurate documentation of subtle metastatic disease and thus appropriate risk-stratification (12). Lastly reduction in dose and duration of chemotherapy being tailored to clinical and biological risk features can prevent ototoxicity and neurotoxicity that also impact cognitive outcomes. It is hard to quantify the impact that each of these advances and modifications of therapy will have on long term sequelae but taken together there will be a preservation of cognitive abilities.

The Cohen manuscript demonstrates that CSI is an essential component of curative therapy for WNT medulloblastoma in addition to surgery and adjuvant chemotherapy (Figure 1). Excellent outcomes for this subgroup of patients is a combination of the biology of the tumor and the delivery of adequate therapy. The refinement in therapy as enumerated above will preserve neurocognition as compared to the prior generation of patients. Fortunately, WNT patients are older so the lower dose of CSI in this age group may spare these patients the neurocognitive decline seen in younger children treated with higher doses of CSI. Pending results of the current studies, further dose reduction of CSI may not be possible without a reduction in cure rate. Prior to planning the next generation of studies, investigators need to document the neurocognitive outcomes of patients treated in the current era and not historical controls.

Table 1: Comparison of standard-risk WNT medulloblastoma dose reduction studies, showing cumulative doses of cisplatin (CDDP), lomustine (CCNU), cyclophosphamide (CPM), vincristine (VCR), focal radiotherapy (RT) and craniospinal irradiation (CSI)

	St Jude SJMB12[a]	SIOP-PNET 5 MBLR[b]	COG ACNS1422[c]	Cohen et al 2023 study[d]	Tata Memorial Hospital Study[e]
CDDP	300 mg/m^2	210 mg/m^2	300 mg/m^2	450 mg/m^2	225 mg/m^2
VCR	8 mg/m^2	18 mg/m^2	27 mg/m^2	45 mg/m^2	18 mg/m^2
CPM	12 g/m^2	6 g/m^2	6 g/m^2	6 g/m^2	6 g/m^2
CCNU	N/A	225 mg/m^2	300 mg/m^2	450 mg/m^2	N/A
RT	Focal RT (51 Gy) & 15 Gy CSI	Focal RT (54 Gy) & 18 Gy CSI	Focal RT (54 Gy) & 18 Gy CSI	No RT	Focal RT (54 Gy) only
Study status	Closed (Completed accrual)	Closed (Completed accrual)	Open	Closed early due to recurrent disease	Closed early due to recurrent disease

[a]NCT01878617 (St Jude; St Jude Children's Research Hospital SJMB12)
[b]NCT02066220 (SIOP-PNET 5 MBLR; International Society of Paediatric Oncology-PNET 5 Medulloblastoma Low-risk)
[c]NCT02724579 (COG; Children's Oncology Group, ACNS1422)
[d]NCT02212574
[e]CTRI/2017/12/ 010767

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Figure 1. The critical role of radiotherapy to cure patients with WNT medulloblastoma, the most favorable medulloblastoma subgroup. Image on the left shaded in blue, reveals how the omission of radiotherapy (cranisospinal and focal boost to the tumor bed) led to rapid disease relapse both at the primary site and also metastatic (depicted as red dots and red circle in the figure) in 100% of patients. This was despite maximal tumor resection and chemotherapy. The middle image shaded in green, shows that delivering a focal boost of radiotherapy to the tumor bed and omitting craniospinal radiotherapy was also inadequate for disease control, with 50% of patients sustaining metastatic relapses along the neuro-axis (depicted as red dots in the figure). This was also in spite of maximal tumor resection and chemotherapy. The image on the right shaded in purple, depicts the excellent disease control achieved using cranisospinal and focal boost to the tumor bed following maximal tumor resection and post-radiotherapy chemotherapy.

Figure 1