Marrow-ablative consolidation chemotherapy and molecular targeted therapy delivered in a risk-adapted manner for newly diagnosed children with choroid plexus carcinoma: *A work in progress*

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Abstract

Choroid plexus carcinomas (CPC) are early childhood cancers characterized by loss of *TP53* function and poor survival. We are analyzing data on *TP53* status, survival, and second cancers from the largest cohort of CPC receiving chemotherapy followed by consolidation with marrow-ablative chemotherapy (HDCx). Additionally, we discuss the rationale for targeted therapies for CPC patients. Currently, 8 of the 13 with Li-Fraumeni Syndrome-associated CPC were treated and continued CPC-free, indicating that HDCx improves CPC-free survival in young children with *TP53*-mutated CPC. These data justify the inclusion of HDCx in the planned prospective international trial for children with *TP53*-mutated CPC.

Keywords

choroid plexus carcinoma | Li-Fraumeni syndrome | marrow-ablative chemotherapy

Choroid plexus carcinoma (CPC) is a rare primary malignant brain cancer that primarily impacts children under the age of 5.[1] Originating from the choroid plexus epithelium, this tumor typically is an intraventricular lesion, often located in the lateral ventricles.

The association of this tumor with the *TP53* germline mutation cancer predisposition syndrome, known as Li-Fraumeni syndrome (LFS), has gained recognition. According to published data, up to 40% of children under 5 years of age diagnosed with CPC develop it in the context of LFS, while nearly 60% of all children with CPC exhibit somatic mutations of *TP53* in the tumor.[1–4] CPC is usually the first cancer to develop in children with *TP53* germline mutations, leading to the identification of a de novo germline *TP53* mutation in those without a family history.

Pathogenesis and the Role of *TP53* Gene Mutations

The pathogenesis of CPC remains poorly understood due to its rarity and lack of representative animal models. However, *TP53* mutations, detected in 50%–60% of CPC patients[1,2,5] are considered crucial in its development. Furthermore, 2 sequence variants (*TP53* codon72 and *MDM2* SNP309) associated with p53 dysfunction were found in 92% of *TP53* wild-type (WT) CPC, indicating an alternative mechanism of p53 dysfunction.

The dysfunction of the p53 protein plays a key role in CPC tumorigenesis and treatment resistance by disrupting the regulation of cellular proliferation and causing genomic instability. Higher numbers of mutant *TP53* copies are linked to increased tumor aggressiveness and unfavorable outcomes,

with a 5-year overall survival of 14% for 2 copies compared to 66% for one copy.[2]

Merino et al. suggested that *TP53* mutations lead to both loss of p53 tumor-suppressive activities and acquisition gain of function oncogenic activities, including cellular invasion, proliferation, and genomic instability that promote CPC development.[2]

TP53 mutations have been linked to hypermethylation at the promoter of the p53-associated microRNA miR-34A in tumors from patients with LFS, correlating with poor survival.[6] This suggests a potential impact of *TP53* mutations on epigenetic dysregulation through miR-34A.

Additionally, the malignant transformation of *T53* mutant choroid plexus papilloma into CPC in a patient with LFS can show genetic alterations linked to an acquisition of a malignant phenotype and thus instrumental in the pathogenesis of carcinoma. This transformation was elucidated in the study by Yankelevich et al.[7] Both original papilloma and subsequent carcinoma had the same *TP53* mutation; however, progressive chromosomal instability, characterized by extensive losses of genetic material including the loss of additional tumor suppressor genes such as *RB* likely marked an important stage in development of CPC.[7] Similarly, it has been shown by Thomas et al. that for supratentorial choroid plexus tumors in young patients, mainly losses in DNA copy-number alterations were prevalent and thus potentially relevant to CPC oncogenesis in this group of patients.[8] When ploidy of CPCs was studied by Merino et al., 60% of tumors were hypodiploid with predominant losses and 40% were hyperdiploid with predominant gains. Notably, in this study, *TP53* mutations were more frequently associated with the hypodiploid than hyperdiploid CPC (88% vs. 47%, respectively).[2] Also, a murine CPC model exhibited multiple chromosomal losses like the hypodiploid human CPC.[9,10]

Other molecular changes have been identified in addition to *TP53* alterations. These include *MYC* overexpression,[9–12] additional losses of *RB* and *PTEN*,[13] telomere dysregulation,[12,14] and shared amplification of some oncogenes in both human CPC and mouse models.[13] These changes are less frequent and persistent compared to *TP53* loss, and as a result, their role in the pathogenesis of CPC is less clear.

Treatment Outcomes

Most reports of treatment outcomes for children with CPC have reflected small patient numbers, retrospective analyses, and, until recently, no recognition or distinction between patients with or without *TP53* germline or somatic *TP53* mutations.

Radiation therapy (RT) has been variably associated with improved disease-free survival. Irradiation-sparing strategies have been reported in limited cohorts of patients. Lafay-Cousin et al. described 8 of the 12 patients treated with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy as radiation-free long-term survivors.[15] Similarly, Zaky et al. described 5 of the 10 children treated with HDCx and autologous hematopoietic progenitor cell rescue (AuHPCR) being alive and irradiation-free at a mean time of 57.6 months from diagnosis.[16] In addition, the prospective randomized study of 2 chemotherapy regimens in patients with newly diagnosed CPC conducted by SIOP

demonstrated long-term survival for 12 out of 33 children less than 3 years of age with CPC treated with surgery and chemotherapy only.[17] However, in these 3 reports, *TP53* status of the tumor was not available.[15–17] Another study indicated improved CPC-free survival for young children with *TP53* germline mutations, utilizing an irradiation-free approach of intensive induction chemotherapy (including high-dose systemic methotrexate) followed by HDCx and AuHPCR[3]: 3 patients with *TP53* germline mutations treated with this approach have remained free of progression at last follow-up between 12 and 84 months from diagnosis.

Few studies with available *TP53* mutation data have indicated poorer disease-free survival for children with germline or somatic *TP53* mutations.[1,3,4,18] The clearest published analysis of treatment outcomes in recent years comes from the small group of children newly diagnosed with CPC enrolled in the prospective St. Jude-based clinical trial SJY07, published in 2021 by Liu et al.[18] Among the 13 children under 3 years of age at CPC diagnosis, 7 harbored *TP53* germline (*n* = 4) or somatic (*n* = 3) mutations. Those with WT *TP53* in both germline and tumor had excellent event-free and overall survival rates of 100%. In contrast, the 7 children with germline or somatic *TP53* mutations had poorer outcomes, with event-free survival (EFS) of only 28.6%. Strong negative prognostic impact of *TP53* mutation status was also confirmed in a recent report by Zaytseva et al. where 5-year OS was 20% in patients with mutated *TP53* vs 82% in WT *TP53*.[4] The presence of *TP53* mutations was also a prognostic factor in patients treated with RT with striking difference in survival (5-year OS of 0% in *TP53* mutated vs. 82% in WT patients).[1]

Retrospective Updated Analysis of *TP53* Mutation Data and Survival in Patients Treated With HDCx and AuHPCR

Starting from June 2023, we have undertaken a systematic effort to gather retrospective outcome data on children with newly diagnosed CPC who were treated with irradiation-sparing strategy. Additionally, *TP53* germline and somatic mutation status and family history of LFS phenotypic cancers were collected. At the time of this report, we have analyzed data on *TP53* status, CPC-free survival and second cancers from the largest cohort of patients who received initial therapy with the intent of undergoing HDCx and AuHPCR. Patients without known outcome data were excluded from the analysis. We used the published data on outcomes in *TP53* mutated patients treated without HDCx consolidation cited above[1,4,18] (5-year EFS of 28%, 5-year OS 20%, and 5-year OS of 0%) as a reference point for comparison of survival outcomes from our retrospective analysis. At the time of this publication, our analysis included 27 patients from multiple institutions in North America, Australia, New Zealand, and Colombia. Table 1 shows demographics, *TP53* mutation data, treatment, and outcomes. Our preliminary findings to date have revealed the following:

- Twenty-seven children with CPC received HeadStart-like induction chemotherapy and 22 completed HDCx consolidation. The reasons for not receiving HDCx included family refusal or rapid disease progression during induction chemotherapy.
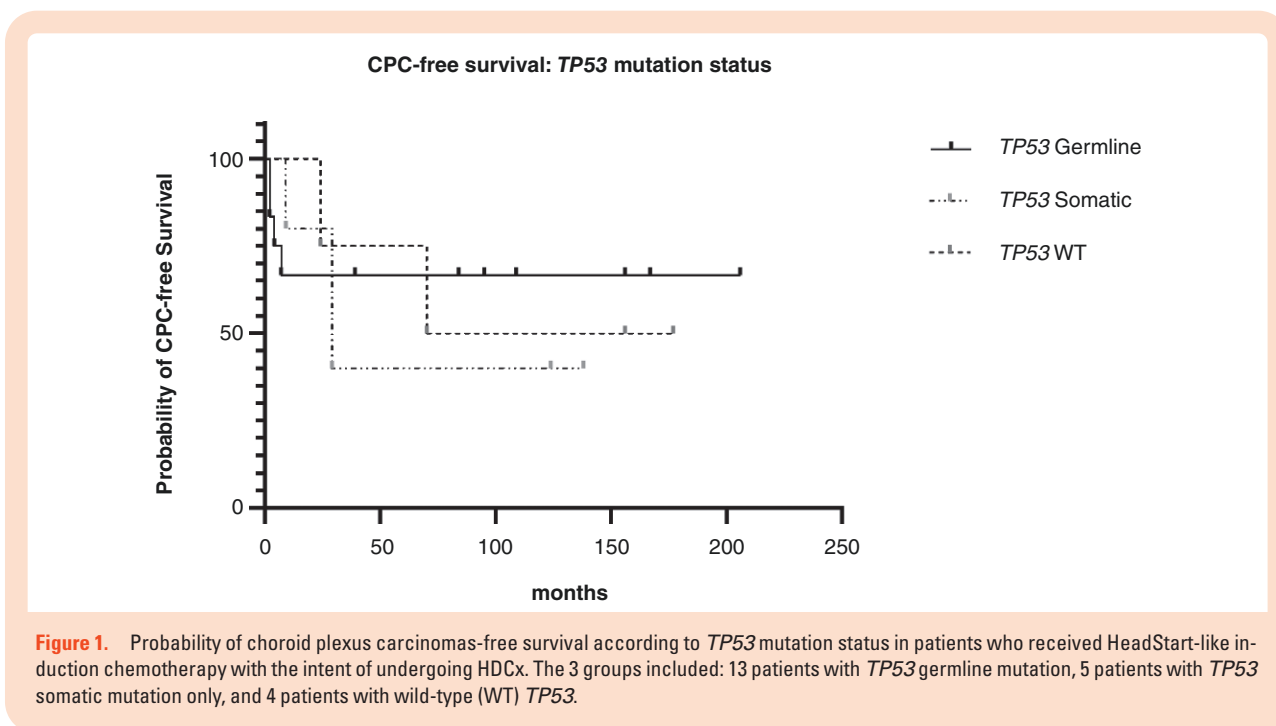
Table 1. *Time From Diagnosis

	Age (mo)/gender	*TP53* Status	Stage	HDCx	Secondary cancer	Outcome*
1	54/M	germline	M0/R0	No, refusal	AML, < 3 years	Died from AML at 39 mo
2	10/M	germline	M0/R0	No, PD	MDS	Recurrence at 4 mo, DOD at 34 mo
3	48/F	germline	M0/R0	No	ACC at 40 mo	Died of ACC at 84 mo
4	12/M	germline	M3/R0	Yes	Sarcoma	Died of sarcoma at 167 mo
5	15/F	WT	M0/R0	Yes	None	Alive NED at 177 mo
6	14/M	germline and somatic	M0/R0	Yes	GCT at 60 mo, OST at 80 mo	Alive NED at 156 mo
7	16/F	somatic	M0/R0	Yes	None	Alive NED at 124 mo
8	11/M	germline and somatic	M3/R0	Yes	None	Alive NED at 94 mo
9	16/F	germline and somatic	M3/R0	Yes	None	PD at 7 mo, DOD at 10 mo
10	26/F	somatic+, germline not tested	M0/R1	Yes	None	Alive NED at 138 mo
11	50/M	WT	M0/R0	Yes	None	PD at 70 mo, DOD at 96 mo
12	10/F	somatic	M0/R0	Yes	None	Alive NED at 29 mo
13	87/M	germline and somatic	M0/R0	Yes	AML at 32 mo	Alive NED at 84 mo
14	36/M	germline and somatic	M0/R0	Yes	OST at 85 mo, ALL at 108 mo	Died of progressive OST and ALL at 109 mo
15	19/M	WT	M0/R0	No, refusal	None	PD at 24 mo, LTFU at 41 mo
16	24/M	NT	M0/R0	No, refusal	None	PD at 38 mo, DOD at 69 mo
17	30/M	NT	M2/R1	Yes	None	PD at 43 mo, DOD at 69 mo
18	32/M	NT	M0/R1	Yes	None	PD at 12 mo, DOD at 29 mo
19	1/F	WT	M2/R1	Yes	None	PD at 13 mo, DOD at 80 mo
20	36/M	germline	M0/R1	Yes	None	PD at 2 mo, DOD at 64 mo
21	4/M	NT	M0/R0	Yes	None	PD at 17 mo, DOD at 55 mo
22	5/M	germline and somatic	M0/R1	Yes	OST at 132 mo	Alive NED at 206 mo
23	28/M	WT	M0/R0	Yes	None	Alive NED at 156 mo
24	67/F	somatic	M0/R0	Yes	None	PD at 29 mo, DOD at 93 mo
25	13/M	somatic	M0/R1	Yes	None	PD at 9 mo, DOD 12 mo
26	18/M	germline	M3/R1	Yes	None	PD at 2 mo
27	4/M	germline	M3/R1	Yes	None	PD at 2 mo

mo, months; WT, wild-type; M0, no leptomeningeal spread; M2, positive cytology; M3, leptomeningeal spread; R0, no residual tumor after resection; R1 > 1 cm residual tumor after resection; AML, acute myeloid leukemia; ACC, adrenal cortical carcinoma; DOD, died of disease; GCT, granular cell tumor; OST, osteosarcoma; MDS, myelodysplastic syndrome; NED, no evidence of disease, NT, not tested; PD, progressive disease;

- Of 27 total patients, somatic ($n = 5$) or germline ($n = 13$) *TP53* mutations were identified in 18 patients and 4 exhibited *TP53* WT. *TP53* status remained untested or unknown in 5 patients. Thirteen patients with LFS-associated CPC (median age 14 months, range 4 to 87 months) included 3 with metastatic disease and 3 with sub-totally resected primary tumor.
- Ten out of the Thirteen patients with LFS-associated CPC underwent consolidation with either a single cycle ($n = 4$) or 2 or 3 tandem cycles ($n = 6$) of HDCx and AuHPCR. Among them, 8 remained CPC-free (80%). Among the 3 patients with LFS-associated CPC who did not receive AuHPCR, 2 developed progressive disease and one died of early-onset AML.
- Overall, 8 out of 13 (62%) LFS patients remained CPC-free; *however, 4 out of 8 died of secondary cancers,* while 4 others developed CPC recurrence/progression.

Median survival time for 18 patients with germline or somatic *TP53* mutations was 84 months. Ten-year CPC-free survival was 62% for patients with *TP53* germline mutations (Figure 1, $n = 12$), 40% for those with somatic tumor *TP53* mutations ($n = 5$) and 50% with confirmed TP53 WT ($n = 4$). Ten-year CPC-free survival for all 18 patients with known germline or somatic *TP53* mutations was 58%. Eight out of twelve patients with *TP53* germline mutations and LFS developed second malignancies 1 to 10 years posttreatment, including 6 patients in HDCx group and the remaining 2 patients who did not undergo consolidative HDCx.

These preliminary data indicate that HDCx consolidation is associated with improved CPC-free survival of 58% at 10 years and OS of 47% at 10 years compared with historical reports in children with either germline or somatic

Figure 1. Probability of choroid plexus carcinomas-free survival according to *TP53* mutation status in patients who received HeadStart-like induction chemotherapy with the intent of undergoing HDCx. The 3 groups included: 13 patients with *TP53* germline mutation, 5 patients with *TP53* somatic mutation only, and 4 patients with wild-type (WT) *TP53*.

TP53 mutated CPC treated without HDCx consolidation (EFS of 28% at 5 years,[18] OS of 20% at 5 years,[4] and OS of 0% at 5 years[1]). The ultimate development of secondary cancers affects outcomes for those with LFS, irrespective of HDCx treatment. These data justify the inclusion of HDCx in the prospective international trial under development for young children with newly diagnosed *TP53* mutated CPC.

Rationale for Innovative, Targeted Treatment Strategies

LFS-associated CPC have been noted to harbor a significantly higher burden of chromosomal structural variations as well as significant risk of progression.[1,2] Furthermore, LFS-associated CPC patients have been reported to display a poorer survival outcome following RT as compared to those with WT *TP53*.[1] Chemotherapy agents used to treat CPCs including etoposide, alkylating, and platinum-based drugs are associated with an increased risk of secondary cancers, and their use should be carefully considered in children with LFS-associated CPC who carry predisposition to multiple primary cancers as well as increased sensitivity to irradiation and chemotherapy-induced carcinogenesis, necessitating the search for innovative therapeutic modalities.

Treatment advances in CPC have been hampered by a scarcity of preclinical studies. There is growing evidence that demonstrates the evolving role of targeted therapy in CPC. Preclinical studies performed on CPC cells have revealed multiple potential therapeutic targets including mammalian target of rapamycin (mTOR), platelet-derived growth factor receptor, ataxia-telangiectasia and Rad3-related protein (ATR), phosphatidylinositol 3-kinase (PI3K), fibroblast growth factor receptor 1 (FGFR1) and cyclin-dependent kinases (CDK).[19–22] To pave the way for novel CPC therapeutic strategies, Martin et al. have recently conducted high-throughput screening of a patient-derived CPC cell line and have identified multiple molecular targets including CDK, PDGF, ATR, FGFR1, PI3K, and mTOR.[22] In this study, 2 combinations using a DNA alkylator (melphalan) or topoisomerase inhibitor (topotecan) in combination with an *ATR* inhibitor (elimusertib) were suggested as potential treatment strategies. These combinations (topotecan/elimusertib and melphalan/elimusertib) were validated both in vitro and in vivo. The mechanisms of synergistic activity for melphalan/elimusertib were assessed through transcriptome analyses and showed dysregulation of key oncogenic pathways (eg, MYC, mTOR, and p53) and activation of critical biological processes (eg, DNA repair, apoptosis, hypoxia, and interferon-gamma) leading to decreased tumor viability and eventually longer survival.

Wang et al. used high-throughput drug screening in their developed mouse models of hypodiploid CPC by activating the *MYC* oncogene and inactivating the *TP53* tumor suppressor in neural stem cell progenitors.[10] They identified pan CDK inhibitors and triptolide as potential therapies for CPC.[10]

Cornelius et al. reported an improved outcome in an infant with relapsed metastatic CPC refractory to salvage chemotherapy, who was treated with molecular-driven targeted therapy[19] guided by genomic profiling of the tumor. The profiling identified not only a *TP53* germline mutation with loss of heterozygosity but also aberrant overexpression of multiple biological pathways including *mTOR*, *PDGFRB*, *FGF2,* and *HDAC*. The patient commenced targeted therapy with sirolimus, thalidomide, sunitinib, and vorinostat achieving a 90% reduction in tumor size with no serious adverse events, excellent quality of life, and long-term survival.

Summary

The poor outcomes observed with conventional chemotherapy and the high incidence of secondary malignancies highlight the need to integrate targeted therapeutics into the treatment of children with recurrent/refractory and potentially newly diagnosed *TP53* mutated CPC. Combined with our preliminary findings demonstrating improved outcomes for children with *TP53* mutation–associated CPC who undergo consolidation with HDCx and AuHPCR, while avoiding RT, these findings provide the rationale for a prospective international clinical trial for children with newly diagnosed or recurrent CPC. In this future clinical trial, currently in an advanced stage of development, patients with newly diagnosed CPC will be treated in a risk-adapted manner. The goal is to use HDCx consolidation in high-risk patients (all patients with mutated *TP53* and those with WT *TP53* who did not achieve a complete response after surgery and induction chemotherapy), while using conventional chemotherapy only for patients with WT *TP53* who achieved CR. Additionally, a separate sub-trial for patients with the recurrent disease will be designed to use targeted therapies based on the patient's molecular tumor testing.

Disclaimer

None.

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Conflict of interest statement

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