Systemic Therapy for Medulloblastoma

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Outline

- Evolution of Chemotherapy in Medulloblastoma
- Principles of chemotherapy
- Optimization of chemotherapy
- Risk Stratification
- Chemotherapy in Average Risk
- Chemotherapy in High risk group
- Chemotherapy in Infants & young children
- Recurrent medulloblastoma
- Future of Systemic therapy

Team Work

100%

Targeted Therapy

Conventional CT
70-80%

RT

50-60% survival

Surgery

10-20% survival

Evolution of chemotherapy

- Pre-1930 era: Surgery alone was used with less than 10% survival and median survival of 12 months
- Bailey and Cushing: pioneered used of whole neuraxis irradiation in 1930 with dramatic improvement in survival to 50-60% by 1980s
- Van EysJ introduced chemotherapy with negative results (Can treat reports, 1981)
- First randomized studies in 1990 by SIOP & CCG established role of chemotherapy in high risk population
- Packer et al in 1999 proved the role of chemotherapy in average risk Medulloblastoma in decreasing the CSI dose with out detriment in survival

Principles of Chemotherapy

- Chemotherapeutic agents should be lipid soluble, less protein bound and less ionized
- Co-administartion of agents decreasing activity through CYPP3A4 induction such as Phenytoin, phenobarbitone and steroids are avoided
- Concomitant RT may be useful by increasing the transcapillary transport

Optimising Systemic Therapy

- Established:
  - high dose chemotherapy
  - Intrathecal therapy
  - Radiosensitizaion
- Experimental:
  - Intratumoral therapy
  - Intraarterial therapy
- Novel approaches:
  - Differentiating agents
  - Gene therapy
  - Antiangiogenesis
  - Targeted agents

Risk-Adapted Approach

Factor	Standard-risk	High-Risk
Age at diagnosis	>3yr	<3 Yr
Extent Surgical resection	<1.5cm^2 Residual	>1.5cm^2 residual
stage	M0	≥M1

Europe: Age and M stage (M1 vs ≥ M2)

Standard-Risk: Traditional Standard

- Maximum surgical resection(GTR)→ craniospinal RT(CSI)± chemotherapy
- RT dose CSI 36Gy, PF dose 55.8Gy
- Chemotherapy is commonly practiced outside a trial
- Preradiation(Neoadjuvant RT/Sandwich) CT in Europe vs Adjuvant in USA
- 75-80% EFS
- High incidence of late neuroendocrine and neuropsychiatric morbidity

Standard-Risk: Trials

Trial	Accrual period	Eligible patients	Treatment (Gy, posterior fossa/ craniospinal axis)	Progression-free survival at 5 years (%)	p
Average risk					
HIT '91	1991–97	118	Ifosfamide, etoposide, methotrexate, cisplatin, cytarabine preradiation (55·2/35·2) *vs* vincristine, lomustine, cisplatin postradiation (55·2/35·2)	65 *vs* 78	<0·03
SIOP III	1992–2000	179	Radiation (55/35) *vs* vincristine, etoposide, carboplatin, cyclophosphamide preradiation (55/35)	60 *vs* 74	0·036
CCG9892	1990–94	65	Vincristine, lomustine, cisplatin postradiation (55·2/23·4)	79	..
SJMB'96	1996–99*	34	High-dose cyclophosphamide, cisplatin, vincristine postradiation (55/23·4)	94†	..
POG8631/ CCG923	1986–90‡	81	Radiation (54/36) *vs* radiation (54/23·4)	67 *vs* 52	0·14§

Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Roger J. Packer, Amar Gajjar, Gilbert Vezina, Lucy Rorke-Adams, Peter C. Burger, Patricia L. Robertson, Lisa Bayer, Deborah LaFond, Bernadine R. Donahue, MaryAnne H. Marymont, Karin Muraszko, James Langston, and Richard Sposto

J Clin Oncol 24:4202-4208.

VOLUME 24 · NUMBER 25 · SEPTEMBER 1 2006

Purpose

To determine the event-free survival (EFS) and overall survival of children with average-risk medulloblastoma and treated with reduced-dose craniospinal radiotherapy (CSRT) and one of two postradiotherapy chemotherapies.

Methods

Four hundred twenty-one patients between 3 years and 21 years of age with nondisseminated medulloblastoma (MB) were prospectively randomly assigned to treatment with 23.4 Gy of CSRT, 55.8 Gy of posterior fossa RT, plus one of two adjuvant chemotherapy regimens: lomustine (CCNU), cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine.

Results

Forty-two of 421 patients enrolled were excluded from analysis. Sixty-six of the remaining 379 patients had incompletely assessable postoperative studies. Five-year EFS and survival for the cohort of 379 patients was 81% ± 2.1% and 86% ± 9%, respectively (median follow-up over 5 years). EFS was unaffected by sex, race, age, treatment regimen, brainstem involvement, or excessive anaplasia. EFS was detrimentally affected by neuroradiographic unassessability. Patients with areas of frank dissemination had a 5-year EFS of 36% ± 15%. Sixty-seven percent of progressions had some component of dissemination. There were seven second malignancies. Infections occurred more frequently on the cyclophosphamide arm and electrolyte abnormalities were more common on the CCNU regimen.

Conclusion

This study discloses an encouraging EFS rate for children with nondisseminated MB treated with reduced-dose craniospinal radiation and chemotherapy. Additional, careful, step-wise reductions in CSRT in adequately staged patients may be possible.

Intellectual Outcome After Reduced-Dose Radiation Therapy Plus Adjuvant Chemotherapy for Medulloblastoma: A Children's Cancer Group Study

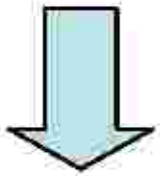
By M. Douglas Ris, Roger Packer, Joel Goldwein, Dana Jones-Wallace, and James M. Boyett

Journal of Clinical Oncology, Vol 19, No 15 (August 1), 2001: pp 3470-3476

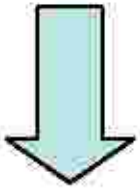
Conclusion: **This study represents the largest series of patients with average-risk MB/PNETs treated with a combination of reduced-dose RT and adjuvant chemotherapy whose intellectual development has been followed prospectively. Intellectual loss was substantial but suggestive of some degree of intellectual preservation compared with effects associated with conventional RT doses. However, this conclusion remains provisional, pending further research.**

Standard-Risk: New Standard

GTR



Reduced dose CSI (23.4Gy)

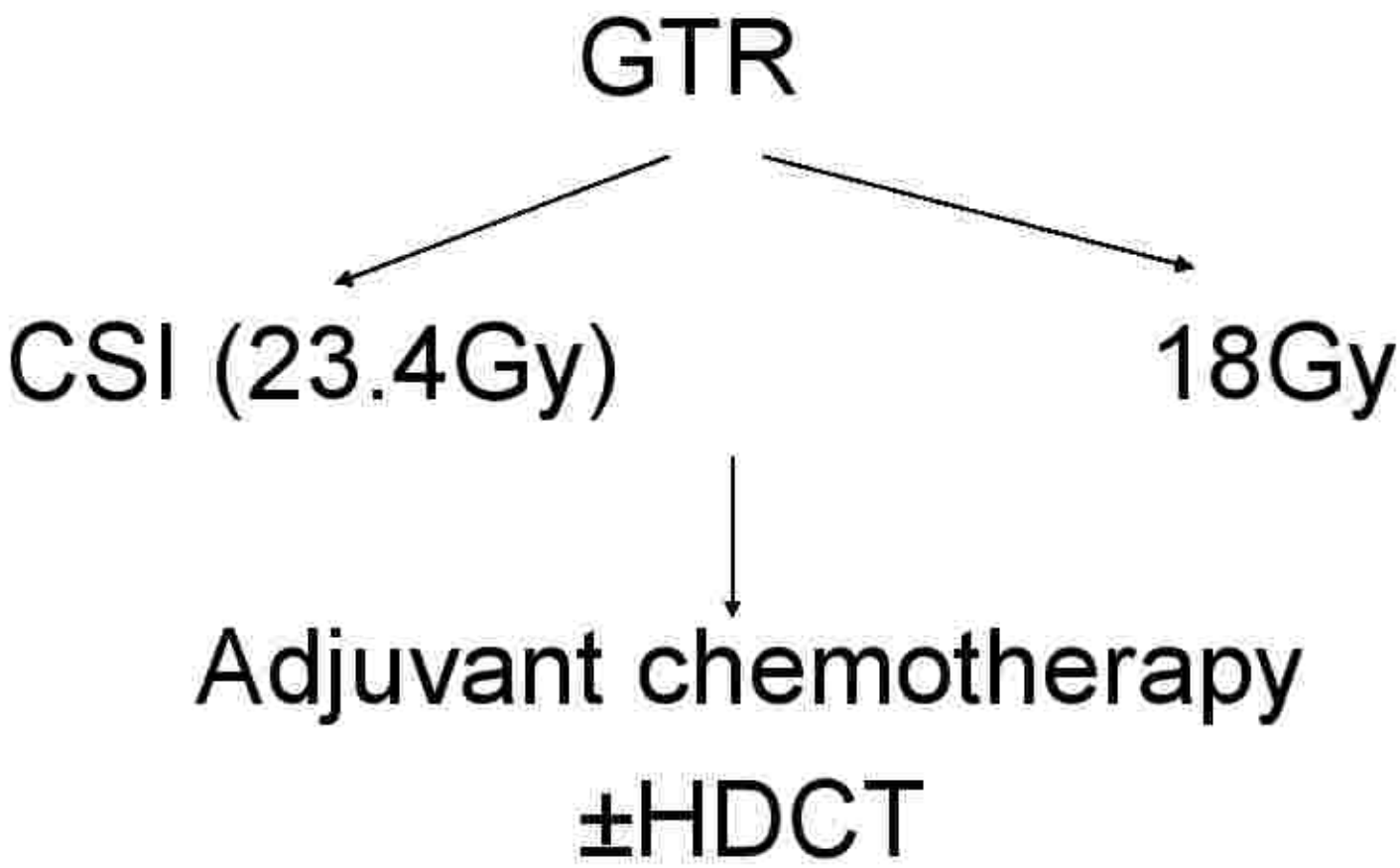


Adjuvant chemotherapy

Chemotherapy when & What?

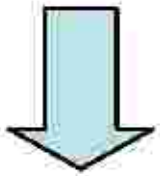
- A range of alkylator and platimum based regimens available
- Adjuvant VCP=Adjuvant VLP
- Other effective regimens:VLCP,VC, VJPE, MICE
- When? NeoAdjuvant CT detrimental (SIOP-II) / inferior to adjuvant CT in average risk (HIT-91)

Standard Risk : Future

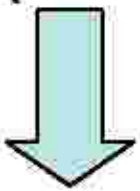


High-Risk: Standard of care

GTR



CSI (36Gy)+PF boost19.8Gy



Adjuvant chemotherapy

Chemotherapy improves survival by 15-20% c/t RT alone historical cohorts

High Risk trials

High risk					
CCG921	1986–92	203	Eight drugs in 1 day preradiation and postradiation (54/36) vs vincristine, lomustine, prednisolone postradiation (54/36)	43 *vs* 63	0·006
SJMB'96	1996–99*	19	Topotecan window preradiation (55/36–39·6) then high-dose cyclophosphamide, cisplatin, vincristine	84†	..
Limited institution CHOP/CNMC/CMCD	1983–93	15	Vincristine, lomustine, cisplatin postradiation (55·2/36)	67	..

High Risk: Neoaduvant vs Adjuvant CT

- Progressive disease rates of 20-30% during neoadjuvant CT in higher M stage
  - (CCG-921)
- Delay in RT detrimental to long term outcome (HIT-91)
- Short neoadjuvant window (6-8 weeks) may be acceptable without any detriment

Feasibility of Four Consecutive High-Dose Chemotherapy Cycles With Stem-Cell Rescue for Patients With Newly Diagnosed Medulloblastoma or Supratentorial Primitive Neuroectodermal Tumor After Craniospinal Radiotherapy: Results of a Collaborative Study

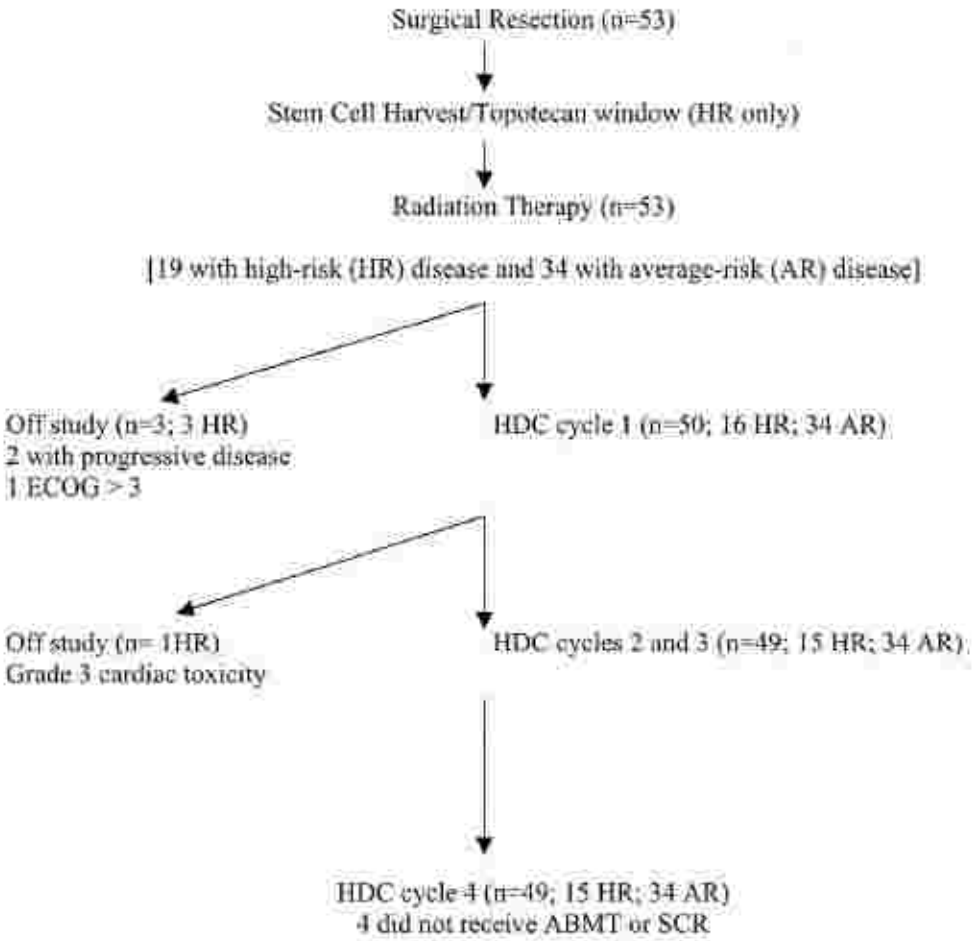
Douglas Strother, David Ashley, Stewart J. Kellie, Akta Patel, Dana Jones-Wallace, Stephen Thompson, Richard Heideman,

Journal of Clinical Oncology, Vol 19, No 10 (May 15), 2001: pp 2696-2704

Results: **Fifty of the 53 patients commenced high-dose chemotherapy, and 49 patients completed all four cycles. The median length of chemotherapy cycles one through four was 28, 27, 29, and 28 days, respectively. Engraftment occurred at a median of 14 to 15 days after infusion of stem cells or autologous bone marrow. The intended dose-intensity of cyclophosphamide was 1,000 mg/m^2/wk; the median delivered dose-intensity was 1,014, 1,023, 974, and 991 mg/m^2/wk for cycles 1 through 4, respectively; associated median relative dose-intensity was 101%, 102%, 97%, and 99%. No deaths were attributable to the toxic effects of high-dose chemotherapy. Early outcome analysis indicates a 2-year progression-free survival of 93.6% ± 4.7% for the average-risk patients. For the high-risk patients, the 2-year progression-free survival is 73.7% ± 10.5% from the start of therapy and 84.2% ± 8.6% from the start of radiation therapy.**

Conclusion: **Administering four consecutive cycles of high-dose chemotherapy with stem-cell support after surgical resection and craniospinal irradiation is feasible in newly diagnosed patients with medulloblastoma/supratentorial PNET with aggressive supportive care. The early outcome results of this approach are very encouraging.**

High Risk: HDCT

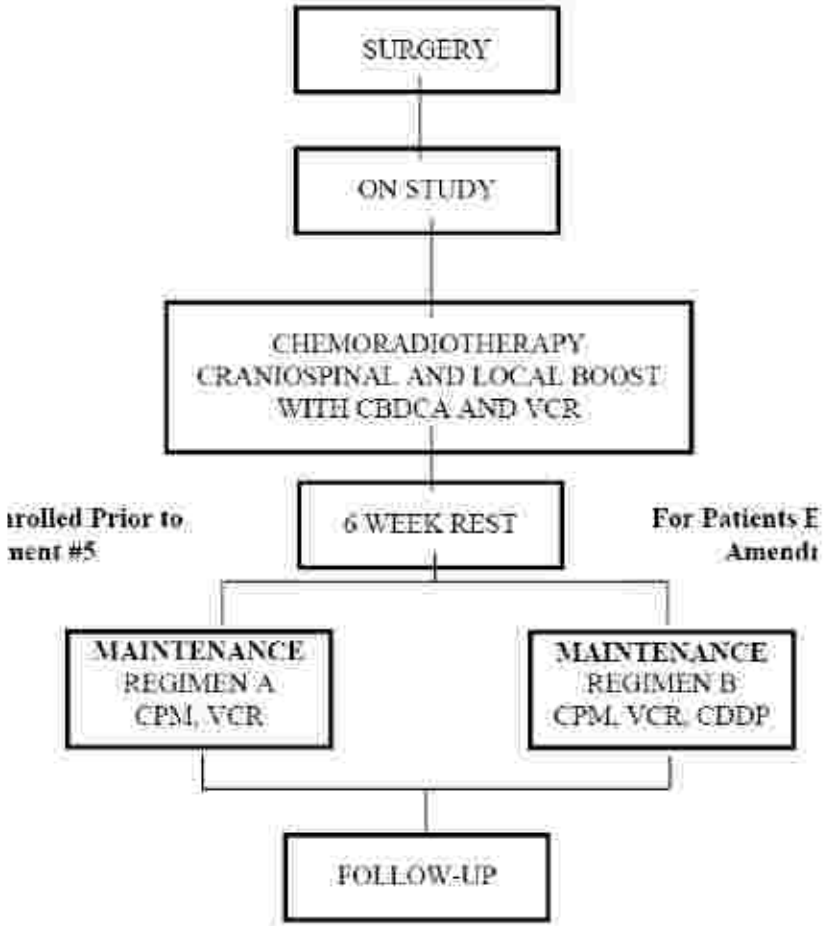


(HDC= high dose chemotherapy; ABMT= autologous bone marrow transplant; SCR= stem cell rescue).

Strother, D. et al. J Clin Oncol; 19:2696-2704 2001

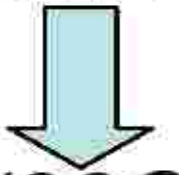
High Risk: Novel approaches: radiosensitization

- CCG-99701

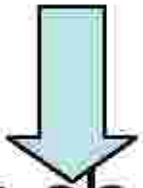


High-Risk: Current trials

GTR



CSI (36Gy)+PF boost19.8Gy±CT



Adjuvant chemotherapy (HDCT) ± biologic therapy

Infants & Young Children(<3 yrs)

- Aim to delay, modify of possibly obviate the need for radiotherapy

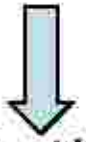
- Chemotherapy alone after surgery-
  - Response rates 30-40%
  - PFS rates 22-40% at 5 years

Infant Trials

Protocol	N	Regimen	Results 5yrPFS	NO RT	Prognostic factor
CCG 9921 (2006)	92	VCPE/VIJE	32%	83%	M1, Residual disease, <1yr
SFOP (2005)	79	PrJ/PE/VC/HDCT	R0M0-29% R1M0-6% R1M1-13%	22%	Residual disease > M1
HIT-92 (2004)	43	VCJM+Itmtx	R0M0-82% R1M0-50% R1M1-33%	53%	Desmoplasia, M+, <2yr

Infant & Young children

- Chemotherapy alone is effective in nondisseminated, totally resected disease
- Current trials
- Induction CT± Intrathecal CT



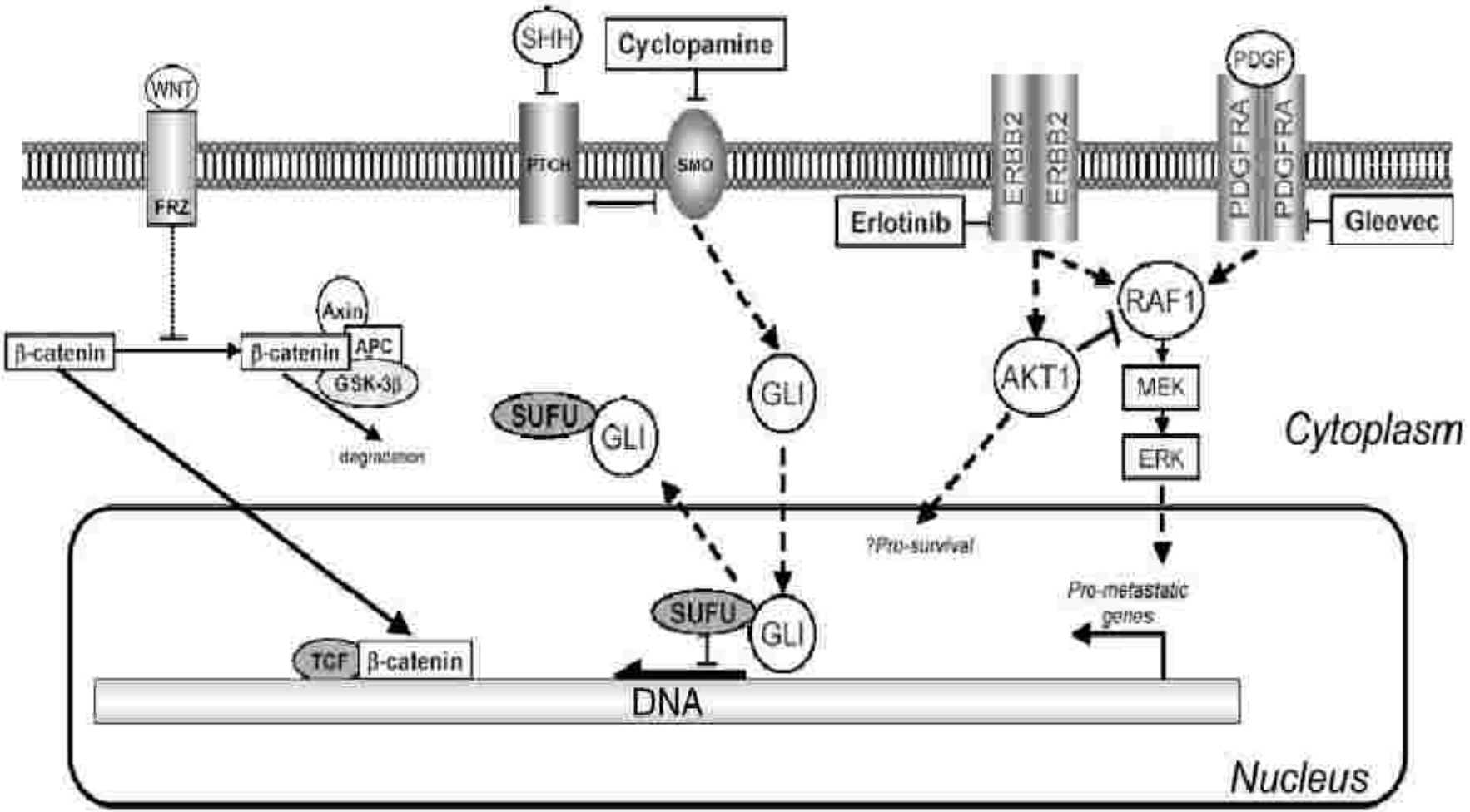
- consolidation CT(HDCT)

- Focal conformal RT (Based on disease status)

Recurrent Medulloblastoma

- Poor prognosis
- Universally fatal till recently
- Trials of single agents or combinations with good initial response but poor long term survival
- Local relapse and chemosensitivity good prognostic factors
- HDCT promising results with 34% EFS in a CCG study with best outcome in patients with minimal residual disease pre-transplant

Novel targeted agents



Status of Novel approaches

Table 3. Active clinical trials utilizing novel therapeutic strategies for embryonal CNS tumors

Novel treatment strategy	Desired effect	Active clinical trials (agent)
HDCT and ASC support	Penetrate BBB, ↑ CNS drug level	COG-99702, high-risk patients, closed; COG-99703, infant patients; POG-9430, recurrent disease
IT chemotherapy	Prevent or treat LM disease	PBTC-001 (mafosfamide); PBTC-005 (busulfan); COG-P9962 (topotecan)
Radiosensitization	↑ RT cytotoxicity	COG-99701 (carboplatin/RT)
BBB disruption	↑ CNS drug level	COG-09716 (carboplatin/lobradimil)
Biologic therapy	Target essential tumor bioactivity	PBTC-002 (VEGFR TKI), closed; PBTC-003 (FTI)
Focal RT	↓ RT neurotoxicity	PBTC-001 (3-D conformal RT)

Abbreviations: ASC = autologous stem cell; COG = Children's Oncology Group; FTI = farnesyl transferase inhibitor; HDCT = high-dose chemotherapy; LM = leptomeningeal; PBTC = Pediatric Brain Tumor Consortium; POG = Pediatric Oncology Group; VEGFR TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

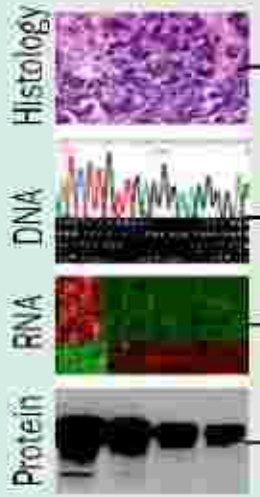
FUTURE OF MEDULLOBLASTOMA THERAPY

Surgery

Neuraxis imaging and cerebrospinal fluid

Tumour

Molecular and histopathological studies



Comprehensive clinical, histopathological, and molecular staging

Low risk → Chemotherapy and 55/18 Gy

Moderate risk → Chemotherapy and 55/35 Gy

High risk → High-dose chemotherapy with or without experimental treatment and 55/36 Gy

Team Work

100%