Determining Risk Features for Medulloblastoma in the Molecular Era

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Since the discovery of medulloblastoma being a compendium of four individual molecular diseases, each with a distinct cell of origin, molecular and clinical features as well as outcome, investigators have attempted to enhance the risk stratification of these tumors to refine therapy[1]. Radiation therapy remains the most effective therapy for medulloblastoma, with attempts to either avoid or reduce the volume of radiation therapy for patients even with the most favorable subgroup, Wingless (WNT) medulloblastoma, resulted in early disease progression[2]. Accurate risk stratification facilitates safe reduction in radiation therapy dose, which is the main adverse factor impacting neurocognitive and neuroendocrine outcomes.

Methylation profiling has further refined Sonic Hedgehog (SHH) medulloblastoma into four subtypes and Group 3 and Group 4 medulloblastoma into eight subtypes. Using advanced genomic tools several investigators have defined risk features in their patient cohorts thus providing a robust risk classification based on several prospectively treated patient cohorts[3,4]. While the specific therapy in each of the patient series differs, the essential treatment components consist of maximal safe surgical resection, cranio-spinal irradiation (CSI) and chemotherapy (whose intensity and timing differs).

In this issue of *Neuro-oncology,* Massimino and colleagues[5] report the long-term outcomes of their Milano-HART (hyperfractionated accelerated radiotherapy) strategy for patients > 3 years old with high-risk medulloblastoma. The strategy involved multiagent high dose chemotherapy cycles, with adjusted HART based on age and response, followed by additional cycles of thiotepa based chemotherapy with autologous stem cell rescue. Their original series which included 33 patients with metastatic disease, reported a 5-year event free survival (EFS) of 70% ±8%, which compared favourably with other approaches[6]. This update describes a total of 89 patients, with the eligibility criteria modified to include large cell/anaplastic histological sub-types, TP53 mutations, and/or *MYC* and *MYCN* amplification to the original clinical criteria. A detailed retrospective analysis of 66/89 patients using methylation profiling further revealed the molecular group and biological risk features. The details of the disease characteristics are presented in Table 1 of their manuscript. This report revealed a 5-year EFS of 66.5%, confirming the originally documented survival rate, and the authors conclude that response to neoadjuvant chemotherapy was the main determinant of survival in this updated series. Other features, such as presence of metastatic disease, *MYC/MYCN* amplification, post-surgical residual disease, histological subtype, CSI dose reduction (31.2 Gy instead of 39 Gy) and omission of radiation therapy boosts, did not significantly impact survival. These findings are provocative and contrary to risk features that have been previously documented in much larger cohorts[1,7,8], including three molecularly annotated prospective clinical trials[3,4,9] (Summarised in Table 1). Despite the long study duration of 20 years, the results must be interpreted with caution due to the relatively small number of patients included in the study. Additionally, the therapy used in this study is different to what is used in most other published series, which may have impacted the results.

Risk features are an interplay between therapy given to a cohort of patients and the molecular features of the tumors in the cohort. The methodology used to determine the molecular features of the tumor also impact the accuracy of the results. Technologies that are currently being used to determine an integrated diagnosis as recommended by the latest version of the WHO

guidelines include histopathological examination (tumor morphology) methylation profiling (group and chromosomal copy number changes); sequencing of the tumor (whole exome or panel sequencing); and germline sequencing (to determine cancer predisposition syndromes). Indeed, in North America, radiotherapy is delivered upfront, followed by different, albeit alkylator based, maintenance chemotherapy regimen. In these studies, the rate of progressive disease during radiotherapy is very low, negating a similar response-based assessment. Integrated diagnosis on a robust prospective trial cohort of patients is most likely to yield risk features that can be interpreted in context of a given therapy. Consequently, caution should be exercised before clinical implementation of a modified risk stratification. Importantly, to this point, the Milano-HART treatment strategy is currently being prospectively tested in one of the arms of the ongoing International Society for Paediatric Oncology-Europe (SIOP-E) high-risk medulloblastoma clinical trial (SIOP-HR-MB)[10], which will definitively confirm or refute their findings.

In summary, evolution of risk features for medulloblastoma is inevitable as treatment modalities change and therapies become further refined. The current report and several other recently published prospective clinical trials, which included extensive molecular analyses, provide opportunities for improved risk classification and treatment refinement. The subsequent series of medulloblastoma trials will incorporate molecular data at diagnosis[3] and the inclusion of serial CSF analysis for the detection of minimal residual disease[11] and provide opportunities for either therapy augmentation or de-escalation.

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Authors' Disclosures

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Table 1 Survival outcomes for high-risk medulloblastoma patients with molecular analyses treated on clinical trials with comparison to the Milano-HART strategy and associated prognostic significance of *MYC/N* amplification and metastatic disease. Also shown is data from multiple large retrospective cohorts of medulloblastoma patients.

Study	Type of Study	n patients	5-year EFS (95% CI) HR MB patients	5-year OS (95% CI) HR MB patients	Prognostic significance of *MYC* amp	Prognostic significance of *MYCN* amp	Prognostic significance of M+ disease
Milano-HART Strategy[5]	Retrospective analysis of uniformly treated series at single institution	89	66.5%	75.9%	Not prognostic	Not prognostic	Not prognostic
St Jude SJMB03[2] **(Only HR MB patients)**	Prospective clinical trial	103	56.7% (4.9%)	69.5% (4.6%)	Inferior survival in Group 3	Inferior survival in SHH	Inferior prognosis in SHH, Group 3 & Group 4
COG 0332[3]	Prospective clinical trial	261	62.9% (55.6-70.2%)	73.4% (66.7-80.1%)	Inferior survival in Group 3	N/R	Inferior prognosis in Group 3
HIT-SKK 2000[9]	Prospective clinical trial	123	62% (52-72%)	74% (66-82%)	*Inferior survival (esp. Group 3)	*Inferior survival	N/A only M+ patients included
#International meta-analysis[1]	Meta-analysis of 7 studies (retrospective)	550 (additional 402 patients in a Validation cohort)	N/A	N/A	Inferior OS in multivariate analysis	Inferior OS in multivariate analysis	Inferior OS
@MAGIC & Int.CC[7]	Retrospective analysis of patients from multiple global centres	1126 (673 in the Discovery cohort) (453 in the Validation cohort)	N/A	N/A	Inferior OS in in Group 3	Inferior OS in SHH	Inferior prognosis in SHH, Group 3 & Group 4 (without Chr11 loss or Chr17 gain)
$European consortium[8]	Retrospective analysis of patients from multiple	704 (428 in the Discovery cohort)	N/A	N/A	Independent negative prognostic marker in	Independent negative prognostic marker in SHH group	Independent negative prognostic marker in SHH group

	centres/studies in Europe	(276 in the Validation cohort)			Groups 3/4 combined		& in Groups 3/4 combined by univariate analysis

Amp amplification, Chr chromosome, CCLG Children's Cancer and Leukaemia Group, COG Children's Oncology Group, UKCCSG-SIOP-PNET3 United Kingdom Children's Cancer Study Group SIOP-PNET3 clinical trial, HR MB high-risk medulloblastoma, Int.CC International Collaborating Centers; MAGIC Medulloblastoma Advanced Genomics International Consortium, N/A Not applicable, N/R Not reported, SHH Sonic Hedgehog group

*MYC/MYCN were combined for survival analysis

$European consortium consisting of UK CCLG, European institutions & UKCCSG-SIOP-PNET3 included only children 0 to 16 years (with both average and high risk medulloblastoma)

@ study included infant, children (with both average and high risk medulloblastoma) and adults

#study included infant, children (with both average and high risk medulloblastoma) and adults