Published in final edited form as:

Pediatr Blood Cancer. 2010 March ; 54(3): 344–345. doi:10.1002/pbc.22398.

High-Risk Medulloblastoma: Does *c-myc* Amplification Overrule Histopathology?

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Medulloblastoma is the most common malignant brain tumor of childhood. Children with non-metastatic disease, age between 3 and 21 years at presentation, and a gross total resection of their primary tumor are classified as standard risk and have an overall survival rate of >80% in a recent large phase 3 trial [1]. Metastatic disease at presentation, young age, and subtotal resection are clinical criteria that portend a worse prognosis [2].

The 2007 WHO classification scheme for medulloblastoma divides this tumor into several subtypes: desmoplastic/nodular medulloblastoma, with islands of tumor showing neuronal differentiation surrounded by more proliferative regions with a reticulin-rich stroma; large cell medulloblastoma, featuring large, round discohesive cells with large nuclei and prominent nucleoli; anaplastic medulloblastoma, with large cells showing marked nuclear atypia and prominent cell/cell wrapping and moulding; and classical medulloblastoma comprised of poorly differentiated small round blue cells lacking specific features [3,4]. There can be substantial overlap between the large cell and anaplastic histology, so the two have frequently been amalgamated into a single category [4,5].

The presence of large cell histology and/or significant anaplasia has been proposed as a poor prognostic factor, a finding that has been upheld by some [2,3,6-9], but not all [1,10] studies. The current Children's Oncology Group study (ACNS0331) excludes patients with significant anaplasia from the standard risk group, and anaplasia without other high-risk features is sufficient for enrollment on a high-risk protocol with intensified therapy (ACNS0332). Large cell/anaplastic histology has been associated with *N-myc* or *c-myc* amplification and/or overexpression [2,5,8], and molecular studies have shown that high expression and/or chromosomal amplification of *c-myc* is a negative prognostic factor in medulloblastoma [2,8,11,12].

In this issue of *Pediatric Blood & Cancer*, von Hoff et al. analyzed outcome data for 28 patients with large cell or anaplastic histology from three European trials. They found that

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young age (<4 years), presence of metastases at diagnosis, large cell histology, and *c-myc* chromosomal amplification were independently associated with negative outcome.

In the absence of other high-risk genetic or clinical factors, severe anaplasia alone was not associated with worse clinical outcomes. Specifically, children whose tumors had anaplastic histology but no *c-myc* amplification, young age, or metastases had a 4-year EFS of 86%, which is superior to that reported in the standard risk group in the HIT'91 trial, one of the trials included in this study [13]. Large cell histology, in contrast, was strongly associated with the presence of *c-myc* chromosomal amplification and poor clinical outcome.

There are several caveats to their findings. Firstly, the number of patients in their study is quite low, with just 12 children in the anaplastic but normal *c-myc* gene dosage group. Secondly, the patients in this study were amalgamated from three cooperative group studies enrolling patients a decade or more ago, and so the patients received non-uniform treatments, potentially skewing the results. Thirdly, there is no comparison to the outcome of nonanaplastic patients with similar risk features in their studies. However, the EFS of 58% of all patients with anaplasia in their study is consistent with that of other recent studies, which reported EFS in patients with significant anaplasia in the 50–60% range [14].

While there has been improvement in outcomes for patients with medulloblastoma over the past 20 years, risk stratification of patients is still in a nascent phase. One of the difficulties of risk stratification based on histologic characteristics of tumor cells is that grading can be pathologist dependent [4]. Using *c-myc* amplification for stratification might therefore remove some of the uncertainty that can arise in histological grading.

However, a number of issues must be resolved before molecular stratification based on *c-myc* can be implemented. It remains unclear whether gene dosage, mRNA level, or perhaps protein expression is the best way to quantify *c-myc* in medulloblastoma. While several studies have shown that *c-myc* amplification measured by FISH is prognostic of decreased EFS, other investigators have found that *c-myc* mRNA levels do not always correlate with *c-myc* gene dosage [8,12]. von Hoff et al. also found that *c-myc* gene amplification was associated with lower EFS but not with *c-myc* mRNA level, and there was no correlation between high *c-myc* mRNA level and poor outcome. This raises the question of whether *c-myc* gene amplification is merely a proxy for chromosomal instability, or if *c-myc*'s function in medulloblastoma is more complex. Immunohistochemical analysis of *c-myc* protein levels would be a straightforward way to examine the functional association between oncogene expression, medulloblastoma histopathology, and outcome, but this assessment of *c-myc* expression will require the development of improved methodologies and reagents to be clinically useful.

An additional challenge for the field is how to meld multiple individual prognostic molecular markers together with clinical and histological data to develop algorithms for therapeutic stratification. While some children with high-risk medulloblastoma may need intensified therapy, another subset of patients may need *less* than standard therapy to cure their cancer. The current standard-risk Children's Oncology Group study in

medulloblastoma is attempting to determine if decreasing the radiation field size and intensity can be accomplished without impacting survival.

In the future, oncologists will increasingly turn to biomarkers that define the key signaling pathways in a tumor and predict response to inhibitors of those pathways. The advent of high-throughput genetic profiling will greatly facilitate the development of such individualized treatment plans, but simpler single gene predictors may play a role as well. In the context of the importance of *c-myc* to medulloblastoma risk stratification, therapeutic agents targeting *c-myc* have recently been tested on medulloblastoma cells [15].

If other studies can validate the finding of von Hoff et al. that *c-myc* amplification status is more accurate than anaplastic histology in predicting outcome, then *c-myc* FISH may be a valuable tool to ensure that children with anaplastic histology receive the most appropriate therapy, allowing them to achieve the most benefit with the least toxicity. These results could then challenge some of the risk-stratification strategies currently being employed by pediatric oncology cooperative groups.

Acknowledgments

The authors thank Kenneth Cohen, MD for his comments on the manuscript. EHR is a fellow of the St. Baldrick's Foundation.

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