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ARAŞTIRMA / RESEARCH

Prognostic and clinical significance of expressions of P53, ERBB2, c-Kit and BCL2 in childhood medulloblastoma

Çocukluk çağı medulloblastom olgularında P53, ERBB2, c-Kit ve BCL2 ekspresyonunun prognostik ve klinik önemi

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Abstract

Purpose: The objective of this study is to evaluate prognostic implications of clinical, histopathological features and immuhistochemical expressions of p53, ERBB2, c-Kit and Bcl-2 in pediatric medulloblastoma.

Materials and Methods: A total of 29 pediatric medulloblastoma cases were evaluated for prognostic association of demographic, clinical, histopathological features and immunohistochemical expressions of p53, ERBB2, c-Kit and Bcl-2.

Results: Median age at diagnosis was 69 months (21-122 months). Median duration of follow-up was 54 months (2-209 months). Fourteen of samples were diagnosed as classical (48%), thirteen cases as nodular/desmoplastic (45%) and two cases as anaplastic (7%) subtype. Staining for c-Kit, Bcl-2, p53 and ERBB2 was positive in 28, 10, 9 and 2 samples, respectively. Overall (OS) and event-free survival (EFS) were 62 % and 52%, respectively. Bcl-2 expression was found to be significantly increased in nodular/desmoplastic subtype. None of the clinical, histopathological and immunohistochemical features were related to survival.

Conclusion: This study reflects the earliest periods of current multimodal treatment protocols of medulloblastoma with similar survival rates in literature. Although none of the proposed factors have been associated with survival, future studies combining molecular and immunohistochemical methods would be more convenient for detecting new prognostic criteria in pediatric medulloblastoma.

Keywords: Medulloblastoma, p53, ERBB2, c-Kit, Bcl-2.

Öz

Amaç: Bu çalışmanın amacı pediatrik medullbolastom olgularında p53, ERBB2, c-Kit ve Bcl-2 ekspresyonunun klinik ve prognostik öneminin araştırılmasıdır.

Gereç ve Yöntem: Toplam 29 medulloblastom olgusu demografik, klinik, histopatolojik özellikler ve immünhistokimyasal olarak p53, ERBB2, c-Kit ve Bcl-2 ekspresyonlarının prognostik anlamı açısından değerlendirmeye alındı.

Bulgular: Ortanca tanı yaşı 69 aydı (21-122 ay). Ortalama takip süresi 54 ay (2-209 ay) olarak belirlendi. Ondört olgu klasik (%48), 13 olgu nodüler/dezmoplastik (%45) ve 2 olgu anaplastik (%7) olarak değerlendirildi. İmmünhistokimyasal olarak 28 olguda c-Kit, 10 olguda Bcl-2, 9 olguda p53 ve 2 olguda ERBB2 pozitifliği gösterildi. Genel sağkalım oranı %62 ve hastalıksız sağkalım oranı %52 olarak bulundu. Bcl-2 ekspresyonunun nodüler/dezmoplastik alt tipte arttığı gösterildi. Klinik, histopatolojik ve immünhistokimyasal özelliklerin herhangi birisinin prognoz üzerinde etkisi gösterilemedi.

Sonuç: Bu çalışma medulloblastom tedavisinde kombine tedavi protokollerinin kullanılmaya başladığı ilk yılları yansıtmaktadır. Sağkalım oranları tanı yıllarına göre literatür ile benzer saptanmıştır. Değerlendirilen klinik, histopatoloijk ve immünhistokimyasal özelliklerin prognozla ilişkisi gösterilemese de, gelecekte moleküler ve immünhistokimyasal yöntemlerin birlikte kullanıldığı çalışmalarla medulloblastom olgularında prognostik faktörlerin saptanmasının mümkün olacağı düşüncesindeyiz.

Anahtar kelimeler: Medulloblastom, p53, ERBB2, c-Kit, Bcl-2.

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INTRODUCTION

Medulloblastoma is the most common malignant brain tumor of childhood. Despite the heterogeneity in clinical findings, prognostic factors and outcome of the patients, in the past it was thought to be a single entity with uniform features and treatment stratification were based on the clinical features as age, extent of resection and presence of metastasis[1,2]. However, better understanding of tumor biology with the advent of molecular techniques has led to identify 4 molecular subtypes of the disease. New classification was based on mutation profiles, structural chromosomal alterations, histology, demographics, and clinical outcome. Group 1 medulloblastoma, the Wnt subtype, is characterized by upregulation of canonical Wnt signalling. Group 2, the sonic hedgehog (SHH) subtype, shows hallmark activation of the SHH-signalling cascade. Group 3, mostly affects infants and children and a common overexpressed pathway was not defined in the pathogenesis of the disease. In the most common type, group 4 medulloblastoma, cells of origin have not been identified yet[3,4,5]. Neither of these subtypes have been involved into the treatment stratifications yet, and except for vismodegib in the SHH subtype, no targeted agents are available for that specific molecular features[6].

In addition to molecular and genetic findings, immunohistochemical characteristics are also proposed to have prognostic implications for medulloblastoma. Immunohistochemical profiling of molecular expressions would also be suggestive for potential use of targeted or biomarker-based therapies in treatment of medulloblastoma[7].

In this study, the expressions of p53, an extensively studied tumor suppressor gene which have a critical role in tumor progression and prognostic significance for numerous cancers[8]; ERBB2, a tyrosine kinase form epidermal growth factor family with a monoclonal antibody actively used in cancer therapy, c-Kit, a proto-oncogen, similar to PDFGR (Platelet Derived Growth Factor Receptor) and proposed to have a role in medulloblastom tumorigenesis and Bcl-2, an anti-apoptotic molecule, also known to be closely associated with the sensitivity to anticancer drugs were evaluated. We aimed to discover the effects of expressions of these well-known molecules on clinical and treatment outcomes of the children with medulloblastoma.

MATERIALS AND METHODS

Medulloblastoma cases, diagnosed and treated at Istanbul University, Cerrahpasa Medical Faculty, Department of Pediatric Hematology and Oncology between January 1986 to December 2007 were retrospectively included into the study. Eighty-four children with medulloblastoma were recorded. Twenty-nine cases with complete demografic, clinical information and treatment data and with adequate tissue samples for immunohistochemical stainings were included into the study. For remaining 55 cases, the most common reason for exclusion was the inadequacy and poor quality of tumor tissue samples for morphological and immunohistochemical evaluation. The study was approved by local ethical committee of Istanbul University (19.06.2006/ 14648–06).

Demographic data, clinical findings for residual tumor after resection, presence of metastases, degree of surgical resection, chemotherapy and radiotherapy were all noted. Patients were stratified according to modified Chang staging as standart and high risk [9].

Histopathological evaluation

Tumor samples were independently evaluated by a neuropathologist and a cytopathologist. Sections from formaline-fixed, paraffine embedded blocks were stained with hematoxylin- eosin. All samples were evaluated for the diagnosis and histopathological subtypes according to The WHO classification of tumors of the nervous system (2000), as classical, nodular-desmoplastic and anaplastic [10]. Presence of anaplasia was also noted for each sample.

All samples were stained for p53, ERBB2, c-Kit and Bcl-2 (Dako. Denmark®). All immunohistochemical stainings were performed on 5 μm depth tissue sections. Presence and percentage of staining and also the strength of staining were noted. Immunoreactivities were evaluated by two pathologists independently and in the presence of disaggreement, the sample was re-evaluated together.

Statistical analysis

Continous variables were summarized as means and standart deviations or medians and interquartile ranges. Categorical and continous variables were

compared using chi-squared and Student's t test as appropriate. The relationship of histochemical features, prognostic factors and survival were visualised using Kaplan Meier curves and significance of difference in survival was assessed using log-rank test. Finally multivariate regression model was fitted including possible predictors of survival. All hypothesis tests were two tailed, a p value less than 0.05 considered signficant.

RESULTS

Median age at diagnosis was 69 months (21-122 months). Nineteen of the cases were male with a male to female ratio of 1.9/1. Seven patients (24%) were diagnosed under 3-years of age. Gross-total resection was performed to 23 (79%) cases with subtotal resection in 6 cases. Twenty-two cases were evaluated as non-metastatic at the time of diagnosis. Seven patients had cytologically or radiologically confirmed craniospinal metastases. All patients above 3-years of age received craniospinal radiotherapy post-operatively. Five out of seven children diagnosed before age 3 were received radiotherapy after 3-years of age. Two children were not given radiotherapy because of the small age. All patients were treated with the same chemotherapy protocol including CCNU, Vincristin, Cisplatin. Median duration of follow-up was 54 months (2-209 months).

Fourteen of samples were diagnosed as classical (48%), thirteen cases as nodular/desmoplastic (45%) and two cases as anaplastic (7%) subtype. In addition to two cases with diagnosis of anaplastic subtype, presence of anaplasia were noted additionally in three nodular/desmoplastic and one classical medulloblastoma. Of six cases with anaplasia, four cases were died of disease.

Staining for c-Kit, Bcl-2, p53 and ERBB2 was positive in 28, 10, 9 and 2 samples, respectively. Immunohistochemically almost all of the samples (28/29) were stained for c-Kit. Staining was strong in 11 samples (40%), intermediate in 13 samples (46%) and slight in 4 samples (14%). Percentage of staining for c-Kit was more than 50 % in 16 samples. Staining was strongly positive (> 90%) for 11/16 cases (Seven nodular/desmoplastic and four classical medulloblastoma cases)

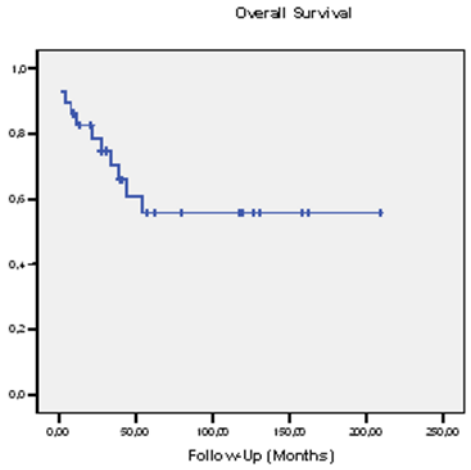

Figure-1. Overall survival, Kaplan-Meier curve

P53 was positive in nine cases with a range of 2-50% (median 5%). ERBB2 was found to be positive only in two samples, so results were not evaluated separately. Bcl-2 positivity was seen in seven samples of nodular/desmoplastic subtype and three samples of classical subtype. Median percentage of staining with Bcl-2 was 25 % (10-90 %). Bcl-2 expression was found to be significantly increased in nodular/desmoplastic subtype *(p=0,04)*. Histopathological and immuhistochemical findings are summarised at Table-1.

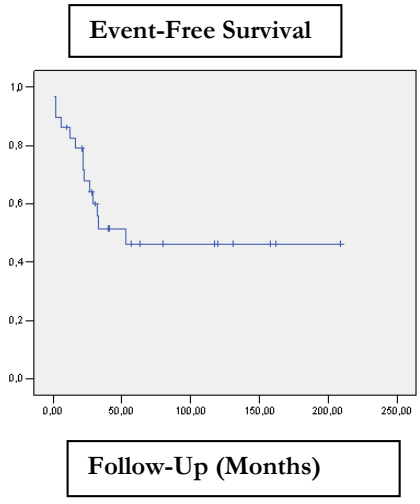

Figure 2. Event-free survival, Kaplan-Meier Curve

Table-1. Histopathological and immunohistochemical findings

Histology	p53 n (%)	ERBB2 n (%)	Bcl–2 n (%)	c-Kit (<50%) n (%)	c-Kit(≥50%) n (%)	Anaplasia n (%)
ND (n=13)	5 (38%)	1 (7%)	7 (54%)	4 (30%)	9 (69%)	3 (23%)
Classical (n=14)	4 (28%)	1 (7%)	3 (21%)	8 (56%)	6 (42%)	1 (7%)
Anaplastic (n=2)	0	0	0	1	1	2 (100%)
Total (n=29)	9 (31%)	2 (7%)	10 (34%)	13 (44%)	16 (55%)	6 (20%)

ND, Nodular/Desmoplastic

Overall (OS) and event-free survival (EFS) were 62 % and 52%, respectively. Median follow-up for overall and event-free survival were 54 months and 45.2 months, respectively. Eleven patients were died of disease with a median follow-up duration of 22.6 months. (2-54 months. Eleven patients (38%) had relapse with a median duration of 24 months after diagnosis. Eight of the relapsed cases were died of the disease. According to subtype, 4 cases with desmoplastic, 6 classical, and 1 anaplastic

Age at diagnosis, amount of resection, presence of metastasis and risk group were not associated with OS and EFS. Although overall survival was similar for both gender, Event-free survival was found to be slightly better for girls.(p=0,04).

Of 11 cases died of disease, 4 cases had nodular/desmoplastic, 6 cases had classical and 1 case had anaplastic subtypes. No significant association was found between demographic features, histopathological subtype, presence of anaplasia and OS and EFS. There was no statistically significant association between immunohistochemical stainings and survival. But regarding Bcl-2 positivity -although survival advantage was not shown - it was remarkable that 10 out of 19 Bcl-2 negative versus 1 out of 10 Bcl-2 positive cases were died of disease.

Age, sex, amount of resection, presence of metastasis, histopathological subtypes and immunhisstochemical features were all included into the multivariate analysis (p<0,5). None of the variables was shown to have an independent effect on OS or EFS (p=0,41).

DISCUSSION

Current treatment protocols of medulloblastoma introduced primarily in 1980s and mainly based on clinical risk stratification and involve multimodal therapeutic approach with combination of surgery, radiotherapy and chemotherapy. These treatment strategies have now resulted in significant improvement overall survival rates of medulloblastoma[11,12].

In our retrospective cohort we found overall and event-free survival as 62 % and 52%, respectively. In the retrospective evaluation of 224 children with medulloblastoma treated between 1975-2006 in a single center from Turkey, Akyuz et al. reported an overall and event-free survival rates of 43% and 41.9%, respectively [13]. Johnston et al. reported a 69.9 % overall survival rate for patients under the age of 18 years diagnosed with medulloblastoma from 1990 to 2009 in Canada [14]. Similarly, Stensvold et al. reported an overall and event-free survival rates of 57 % and 52 %, in the retrospective analysis of medulloblastoma cases under 20 year of age diagnosed between 1973-2013 in Norway [15]. On the other hand, the most recent Children's Oncology Group (COG) study for medulloblastoma, 5 and 10-year event-free survivals were 81 ± 2% and 75.8 ± 2.3%; overall survivals were 87 ± 1.8% and 81.3 ± 2.1% [16]. Although our survival rates are worse than these current studies, it is still compatible with the results of the other retrospective studies with similar time periods of inclusion.

Our study did not show a difference in survival based on the metastatic disease and the risk groups. In the recent Children's Oncology Group (COG) studies for standard-risk and metastatic medulloblastoma, no significant difference in survival was reported, proposing that metastatic stage did not influence survival[17]. Also the overall and event-free survival rates were reported to be 62 % and 74% in prospective multicenter trial HIT 2000 for patients with metastatic medulloblastoma, confirming that metastatic group do not uniformly have poor outcomes and subgorup status and biologic parameters are important in prognosis[18,19]. We think that the results of our study likely reflect intensity of therapy and also suboptimal staging and stratification given the retrospective nature of the study.

In different studies a better survival for desmoplastic nodular subtype and a worse outcome for anaplastic subtype has been reported[18,19,20]. But histopathological subtypes were not associated with survival in our study. We could not draw such a distinction because we had small number of cases to evaluate - only 2 cases of anaplastic medulloblastoma.

Different results were reported in literature regarding the association between p53 expression and survival in medulloblastoma. Jaros showed, by multivariate analysis, that overexpression of p53 enabled identification of a group of MB patients with a sevenfold greater risk of death [21]. Ray and colleagues found that p53 immunoreactivity was predictive of poor outcome in a large group of MB patients [22]. Experimental studies also propose that p53 protects against drug-induced cell death in medulloblastoma cells and play role in chemotherapy resistance [23]. However, in few other studies p53 expression was

not statistically associated with patient survival [24]. In a recent report, Gessi et al. have demonstrated that p53 analysis enables reliable prediction of prognosis for high-risk MB (M?) patients in the multi-centre HIT-2000 trial (8). In our study we did not find any relation between p53 staining and survival, propably because of the small number of the samples.

ERBB2 immunoreactivity in medulloblastoma has been reported in several studies with ambigious results as the relationship to prognosis is concerned. Gilbertson et al. have demonstrated that protein ERBB2 is expressed in most medulloblastomas and associated with poor survival[25,26]. Many other studies have proposed that high expression levels of the ERBB2 along with ERBB2 receptor genes as an independent prognostic marker in childhood medulloblastomas[27]. This oncoprotein has been thought a promising potentiality in future strategies for diagnostics and targeted therapy for these patients as well[28]. In our study only 2 cases were positively stained with ERBB2. This discrepancy with literature may be related to the difficulties in detection of staining due to morphological diversity.

Increased c-Kit expression has been described in pediatric medulloblastoma cells but no any relation to survival was reported[29]. Virag et al found that all medulloblastoma cases displayed abundant tumor cell expression of PDGFR confirming previous studies that indicated the importance of PDGFR signaling[30]. But it seems that c-Kit oncoprotein expression in medulloblastoma is not correlated with activating mutations in the c-Kit exons[30,31]. In our study almost all samples were c-Kit positively with strong staining in more than half of the samples. But we did not find any association with survival. Due to potential therapeutic role of PDFGR inhibitors, further preclinical and biomarker driven clinical investigations needed to understand the mechanism of widespread expression of c-Kit and the exact role in tumorigenesis of medulloblastoma .

Bcl-2, an antiapoptotic protein, is being studied in medulloblastoma for a long time. However, there are controversies about its role in medulloblastomas. Bcl-2 overexpression is proposed to take role in tumor induction and drug resistance[32,33]. Schüller et al. reported an increased expression of Bcl-2 in desmoplastic subtype of medulloblastoma and also a worse outcome for Bcl-2 positive classical medulloblastoma[34]. Similarly, we found a statistically significant increase in Bcl-2 expression in nodular/desmoplastic subtype in our study. We could not demonstrate any relation between Bcl-2 expression and survival in our study but we think this is the result of the small number of the cohort.

This study has major restrictions. The number of cases included was small to define significant statistical differences for proposed clinical and molecular prognostic factors. Also the retrospective nature of the study with histological and immunohistochemical evaluation of the old tissue samples has probably resulted in the different molecular findings from the literature.

Overall, this retrospective study reflects the earliest periods of current multimodal treatment protocols of medulloblastoma with similar survival rates to literature. Although its clinical and prognostic importance have become clear, the routine use of molecular subtyping of medulloblastoma is very challenging in low/middle income countries given its high cost and the need for experienced neuropathologists. Future studies combining molecular and immunohistochemical methods would be more convenient for detecting new prognostic in pediatric medulloblastoma.

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