MIB-1 and p27Kip1 Expression in Nephroblastoma

To the Editors: We read with interest the recent article by Ghanem and coworkers (1) describing the prognostic significance of MIB-1 and p27Kip1 immunostaining in Wilms tumor. The authors report that blastemal MIB-1 and p27Kip1 positivity was prognostically significant for clinical progression and tumor-related death by univariate analysis and that blastemal MIB-1 and p27Kip1 were significant independent prognostic variables for clinical progression in the Cox proportional hazards model. The potential of such markers to identify those patients who may go on to relapse is an attractive one, and studies such as this one are welcome. However, we feel that there are several points in the study that ought to be addressed.

The authors’ cohort of 62 patients were treated according to the International Society of Pediatric Oncology protocols 9 or 93-01, i.e., they received neoadjuvant chemotherapy before nephrectomy. Although it is stated that the samples showed the presence of blastemal, epithelial, and stromal cells, and that careful assessment of the immunohistochemical staining in these different cellular components of the tumor was carried out, nowhere is the actual histologic subtype given. This is of direct clinical relevance because the data from these trials demonstrated the prognostic significance of histologic subtype, with those tumors exhibiting a predominance of blastemal cells after chemotherapy now considered high risk (2). This forms the basis, along with stage, of treatment decision-making in the current SIOP WT2001 clinical trial (3, 4).

What is unclear is how many of the tumors in the series of Ghanem et al. that show a positive blastemal immunoreaction are of this blastemal type, or whether smaller foci of remaining blastemal cells in another histologic subtype are of this blastemal type, or whether smaller foci of remaining blastemal cells in another histologic subtype (low/intermediate risk) are being identified in this way. If this is the case, then interpretation on that basis would greatly strengthen the conclusions of the study. The authors have published previous studies regarding immunohistochemical prognostic factors in Wilms tumors, and it is from here that clues may be gleaned. They have published work on WT1, EGR1 (5); BCL-2, BAX, BCL-Xs,s (6); and CD44 (7) isoforms; each in a series of 61 Wilms tumors that, presumably, must be identical, because they have the same clinical characteristics (29 female, 32 male; mean follow-up, 5.7 years; mean age at operation, 4.2 years; 14 patients showing clinical progression, 8 patients died of disease). They have also analyzed EGFR, TGFα, ERBB2 (8); VEGF, and FLT-1 (9) in a series of 62 Wilms tumors, presumably the one used in the current study (26 female, 36 male; mean follow-up, 5.7 years; mean age at operation, 4.7 years; 14 patients showing clinical progression, 7 patients died of disease). What is not clear is the extent of overlap between these patient study groups. In one report investigating the 62-patient set (9), the tumors are reported to be of all low or intermediate risk according to the earlier SIOP definitions, which includes the blastemal type (10). In another report, studying the 61-patient cohort (5), no histologic subtype is provided; however, the authors report 25 patients with “large amounts of blastema.” In no other publication is the histologic subtype given.

What is particularly unhelpful is the fact that none of these previous publications are cited in the present study. This also raises the question of why no correlations have been published between the different markers reported in the different reports, given the presumed overlap between the datasets. Because it is a positive immunoreaction in the blastemal component of the tumors that tends to show prognostic significance, staining positively in 34% to 61% of tumors across all markers published, it would be of great interest to probe the associations among these data and perhaps develop a more robust model based on a combination of markers. For example, in the present study, the authors report an inverse correlation between MIB-1 and p27Kip1 expression; however, both antibodies seemed to identify six or seven patients who died of their tumor (which presumably means that at least five of these were positive for both), hence their lack of independent prognostic significance for survival. It would be important, if a new marker were to be regarded as providing independent prognostication, for such correlations to be carried out and published across the whole, very valuable, dataset that the authors have accumulated. Finally, the clinical data as presented in the Kaplan–Meier survival curves are also of interest. It appears from the graphs that almost one half of the events occurred after 5 years, although precise data are not given. This is an unusually late pattern of relapse for Wilms tumor, in which the majority of relapses occur within 2 to 3 years of original diagnosis (11). Such a markedly different cohort of patients should be commented on.

Although we are encouraging of work aimed at identifying novel markers of clinical outcome in favorable histology Wilms tumor, we feel that known prognostic variables such as tumor histology ought to be taken into account in the analysis of such experiments. Furthermore, the use of survival analysis, such as the Cox proportional hazards model, to identify independent prognostic variables, when only tumor stage and the markers under investigation are placed in the model, despite the authors’ own publications reporting other significant covariates in the same population, is unwarranted.

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REFERENCES
In Response: With great interest we read the letter of Drs. Jones and Pritchard-Jones discussing our article (1) about prognostic factors in Wilms’ tumor. We agree that the issue of the histologic subtypes of the nephroblastomas is of direct relevance for our analysis. After review of the 62 nephroblastosomas, it appeared that three tumors were of the blastematous (high-grade) subtype. This same population was under study for the potential impact of the different markers, as described in the various articles published. We feel that this small number of high-grade nephroblastomas did not influence the outcome of our studies.

Although we attempted to carry out an analysis of all clinically relevant markers to empower their prognostic value, statistically this proved to be complicated.

Concerning the Kaplan–Meier curves of progression-free intervals, we would like to mention that no selection of patients occurred. All of the children with a Wilms’ tumor were treated according to standard Society International of Oncology Pediatric guidelines as referred to in the article. We fully agree that, on the average, the majority of patients show a relapse within 2 to 3 years after initial diagnosis. However, in studies of relatively small groups of patients, such as the one of the MIB-1 and p27Kip1 markers published by us, inclusion of a very small number of patients having a late relapse, leads to graphs showing late overall patterns of relapse.

Finally, we agree that it would be more appropriate to report on a novel prognostic marker after taking into account the outcome of previously studied markers. However, from a practical point, it used to be more feasible to study larger series of tumors with a few markers at a time. The current availability of the tissue array technology may, to some extent, circumvent this practical problem.

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REFERENCE
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