

HIGHLIGHT

by Katherine K. Matthay*

Is Liver Metastasis in Neuroblastoma an Indication for Treatment Reduction?

In 1971, D'Angio, Evans, and Koop reported a special favorable pattern of metastasis in infants with neuroblastoma that included metastasis to the liver, skin, and bone marrow, which was designated 4s, and frequently regressed without cytotoxic therapy [1]. Subsequent reports and prospective studies verified that stage 4s neuroblastoma, with or without liver involvement, resolved in up to 50% of the cases without requiring cytotoxic therapy [2–4]. Liver involvement in stage 4s did not influence event-free survival (EFS) [3]. A subsequent analysis of 648 patients with metastatic neuroblastoma entered on CCG studies from 1989–1996 showed that liver metastases were associated with a more favorable outcome overall, but in infants predicted a slightly greater EFS and were associated with non-amplified *MYCN* and favorable Shimada, while in children >1 year at diagnosis, liver metastases were an unfavorable prognostic marker and associated with *MYCN*-amplified tumors [5]. Thus, there is some doubt as to whether liver metastases are actually a surrogate for a different tumor biology or an independent prognostic factor, and it remains an enigma as to why tumors metastasizing to this site appear to be less favorable in older children than infants.

Other investigators have focused on the presence or absence of bone metastases as an important prognostic marker or biologic surrogate in neuroblastoma metastasis. Bone metastases in infants or in older children were unfavorable and correlated with unfavorable tumor biology regardless of age [5]. Infants with evidence of bone metastasis on plain radiographs had an unfavorable EFS compared to those with evidence of bone metastases restricted to ¹²³I-MIBG scan or ^{99m}Tc scan [6]. This distinction was used as the basis for the recently completed European study of infant neuroblastoma (NB 99.2) in which infants with stage 4 disease but without radiographic bone metastases were observed rather than treated with chemotherapy. The results are still pending.

In the current issue of *Pediatric Blood and Cancer*, Kushner et al. allocated their stage 4 infants without bone metastases to observation rather than cytotoxic therapy. Kushner et al. further suggest that liver metastases in infants may be an indication for treatment reduction, even in infants with stage 4 neuroblastoma and bone metastases. The investigators report four infants with stage 4 neuroblastoma with liver metastases but no bone metastases, treated with little or no chemotherapy, and all four infants are all surviving. These patients lend credence to the many reports of spontaneous regression in infant neuroblastoma of lower stage tumors and stage 4s tumors and the occasional reports of spontaneous regression in infants with stage 4 neuroblastoma as well as the rationale for the European infant study. Kushner et al. also report six other infants with stage 4

disease with bone metastases and liver metastases, of whom five are surviving in remission but after intensive combination chemotherapy. This outcome is comparable to that previously reported by the Children's Oncology Group (COG) for all infants with stage 4 NB without *MYCN* gene amplification [7] with a shorter but more dose intensive course of chemotherapy. Although the patients in the Kushner report had the unfavorable biologic features of 1p LOH, diploid DNA index, and unfavorable Shimada, they all lacked *MCYN* gene amplification, the overriding factor currently known to be an independent determinant of poor prognosis in stage 4 infants.

It is likely that there are other subsets of patients with stage 4 neuroblastoma for whom treatment reduction is indicated. The authors mention the recent analysis by the COG showing that toddlers of age 12–18 months with favorable biology may have a prognosis equal to that of the younger infants, such that these patients may no longer be candidates for myeloablative therapy [8]. The independent prognostic significance of liver metastasis in early childhood neuroblastoma may be definitively determined by several ongoing studies including (1) analysis of the recently completed European infant study on *MYCN* non-amplified neuroblastoma with treatment stratified by bone metastases, (2) the just-completed COG A3961 study of non-amplified infant stage 4 neuroblastoma that included several molecular biologic factors such as LOH 1P and unbalanced loss of 11q, and (3) the newer expression microarray analyses that will allow multivariate analysis of the prognostic significance of biologic features and metastatic sites.

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¹University of California San Francisco and UCSF Children's Hospital, San Francisco, California

*Correspondence to: Katherine K. Matthay, UCSF Children's Hospital, University of California San Francisco School of Medicine, San Francisco 94143-0106, CA.

Received 29 August 2005; Accepted 29 August 2005

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