NEWS

CLUSTERIN INHIBITS APOPTOSIS BY INTERACTING WITH ACTIVATED BAX.

In this manuscript Zhang et al described the mechanism by which clusterin inhibits apoptosis. Clusterin is a glycoprotein that is overexpressed in several human tumors, including prostate and breast cancer and also head and neck carcinoma. This protein has been previously described as an apoptosis inhibitor, but the mechanism had not been described. Inhibition of clusterin expression sensitizes human cancer cells to chemotherapeutic drugs mediated apoptosis. In this report it is described that clusterin interferes with bax activation at the mitochondria. In contrast with other inhibitors of bax, clusterin interacts with conformation-altered bax in response to chemotherapeutic drugs. Such interaction prevents bax oligomerization thus interfering with the release of citochromme C from mitochondria and therefore caspase activation. Clusterin inhibits also myc-induced apoptosis also by interfering with conformation altered bax. Consequently clusterin promotes myc mediated transformation in vitro and tumor progression in vivo. The results presented in this article suggest that the increased levels of clusterin in human cancer may contribute with oncogenic transformation and cancer evolution.

HYPERDIPLOIDY PLUS NONAMPLIFIED MYCN CONFERS A FAVORABLE PROGNOSIS IN CHILDREN 12 TO 18 MONTHS OLD WITH DISSEMINATED NEUROBLASTOMA: A PEDIATRIC ONCOLOGY GROUP STUDY

Despite the utility of tumor cell ploidy and other biologic variables in assigning infants to risk-based therapies, comparable progress has not been achieved in older children with metastatic tumors, whose 5-year survival rates still range from 15% to 40%. This study tries to determine the predictive strength of tumor cell ploidy and MYCN gene amplification on survival of children older than 12 months with disseminated neuroblastoma (NB).

Of 618 children with stage D NB enrolled onto the Pediatric Oncology Group NB Biology Study 9047 (1990-2000), 560 children were assessable for ploidy and MYCN amplification. Treatment of patients older than 12 months varied; most receiving high-dose chemotherapies with stem-cell rescue. Infants received standard chemotherapy, depending on MYCN status and ploidy.

Among stage D MYCN-amplified patients, 4-year EFS for those with tumor hyperdiploidy was clearly superior to those with diploidy: younger than 12 months or 12 months old. However, among stage D nonamplified-MYCN patients, 4-year EFS for those with tumor hyperdiploidy was clearly superior to those with diploidy: younger than 12 months, 83.7% ± 4.6% versus 46.2% ± 13.8% (P = 0.0037); and for 12- to 24-month-old children, 72.7% ± 10.2% versus 26.7% ± 15.2%(P = 0.0092). Further analysis suggested better prognoses in the 12- to 18-month-old subgroup with hyperdiploid tumors (4-year EFS, 92.9% ± 7.2%) compared with the 19- to 24-month-old subgroup (4-year EFS, 57.9% ± 21.0%; P = 0.007). In children older than 24 months, outcome was dire (< 20% long-term survival), regardless of ploidy or MYCN status.

In conclusion, children 12 to 18 months old with metastatic NB had favorable outcomes with high-dose therapy if their tumors were hyperdiploid and lacked MYCN amplification. This subgroup may respond well to contemporary chemotherapy, and could be spared intensive myeloablative therapy with stem-cell rescue.

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PROPHYLACTIC THYROIDECTOMY IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A

Medullary thyroid carcinoma is the most common cause of death in patients with multiple endocrine neoplasia type 2A (MEN-2A), or type 2B, or familial me-
dullary thyroid carcinoma. The authors sought to determine whether total thyroidectomy in asymptomatic young members of kindreds with MEN-2A who had a mutated allele of the RET proto-oncogene could prevent or cure medullary thyroid carcinoma. In the present study a total of 50 patients 19 years of age or younger who were consecutively identified through a genetic screening program as carriers of a RET mutation characteristic of MEN-2A underwent total thyroidectomy. Five to 10 years after the surgery, each patient was evaluated by physical examination and by determination of plasma calcitonin levels after stimulation with provocative agents. In 44 of the 50 patients, basal and stimulated plasma calcitonin levels were at or below the limits of detection of the assay. Two patients had basal and stimulated plasma calcitonin levels above the normal range. Stimulated plasma calcitonin levels had increased but remained within the normal range in four patients. The data suggest that there was a lower incidence of persistent or recurrent disease in children who underwent total thyroidectomy before eight years of age and in children in whom there were no metastases to cervical lymph nodes.

In conclusion, young patients identified by direct DNA analysis as carriers of a RET mutation characteristic of MEN-2A had no evidence of persistent or recurrent medullary thyroid carcinoma five or more years after total thyroidectomy. A longer period of evaluation will be necessary to confirm that they are cured.