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Nucleophosmin Mutations in AML: A Retrospective Study

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Introduction: Mutations in the nucleophosmin (NPM1) gene have been implicated as a prognostic indicator for cytogenetically normal AML patients. Reportedly, patients harboring a 4bp duplication in exon 12 of NPM1 (in the absence of concomitant Fms-like tyrosine kinase receptor-3 (FLT3) gene internal tandem duplication-ITD) respond more readily to induction chemotherapy and do not appear to benefit from allogeneic transplant. Based on these findings, we performed NPM1 testing on AML patients previously referred to our lab for FLT3-ITD analysis. **Methods**: Of 343 samples representing 191 patients referred to our laboratory for FLT3 analysis, 57 (29.8%) had morphologic or laboratory findings consistent with involvement by AML at the time of submission. PCR amplification for exon 12 of NPM1 was performed on banked DNA, amplicons were separated by capillary electrophoresis and analyzed using GeneMapper v3.7 software (Applied Biosystems, Foster City, CA). The ratio of the NPM1 and FLT3 mutant/wild type alleles were calculated using corresponding peak heights. Forty-five variables were collected from retrospective medical chart review. Statistical analysis was performed using Kaleidograph v4.0 software (Synergy Software, Reading, PA). **Results**: Fourteen of 57 (25%) patients were positive for the NPM1 4bp duplication; 16/57 (28%) were FLT3+; and 6/14 (43%) were NPM1+/FLT3+. Ten of 14 (71%) NPM1+ patients, 9/16 (56%) FLT3+ patients, and 12/33 (36%) NPM1-/FLT3- had morphologically negative 14 day bone marrows. Relapse among NPM1+/FLT3- patients was significantly lower ($P<0.05$) than NPM1-/FLT3+ or NPM1+/FLT3+ patients. Median NPM1 mutant/wild type and FLT3 mutant/wild type ratios at initial detection were 0.35 and 0.0989, respectively. **Conclusions**: The number of NPM1+ and FLT3+ AML patients identified was similar to that reported in other studies. No significant difference was observed between the proportion of negative 14 day bone marrows in NPM1+/FLT3-, NPM1-/FLT3+ or NPM1+/FLT3+. It was observed that NPM1+/FLT3- patients have longer disease-free survival than FLT3+/NPM1- or NPM1+/FLT3+ patients. Lastly, unlike FLT3+ pediatric patients, our initial findings suggest that there is no association between clinical progression of disease and FLT3 or NPM1 mutant/wild type ratios in our adult patients.