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NONINVASIVE GENOTYPING USING DIGITAL PCR BEFORE AND AFTER COMBINATION THERAPY WITH GEFITINIB AND Pemetrexed (PEM) OR S-1 FOR NON-SMALL CELL LUNG CANCER (NSCLC) RESISTANT TO EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) TYROSINE KINASE INHIBITORS (TKI)

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Aim: Repetitive genotyping is useful to assess the genetic evolution of NSCLC during the treatment course, but the need for a biopsy is a major barrier. Digital PCR is a promising procedure for the detection of mutant alleles in the plasma of cancer patients.

Methods: This prospective study enrolled patients with NSCLC harboring known EGFR mutations and who had experienced disease progression during ongoing EGFR-TKI therapy. Eligible patients received daily gefitinib (250 mg) and either PEM (500 mg/m²) or S-1 (80 mg/m², day 1-14). The treatment was repeated every 3 weeks until disease progression or unacceptable toxicity. Plasma was collected before and after the combination therapy, and digital PCR was performed to assess EGFR L858R, exon 19 deletions and T790M. Serum hepatocyte growth factor (HGF) was measured along with tumor evaluation.

Results: From May 2012 to January 2014, nine patients were enrolled. Median age was 67 (range, 52-80) years, and seven patients were female. EGFR mutations at the time of disease diagnosis included L858R in six patients and exon 19 deletions in three patients. Patterns of disease progression during adjacent EGFR-TKI therapy were acquired resistance in seven patients, and primary resistance in two patients. Known EGFR mutations were detected in plasma samples from six (67%) patients at study enrollment. Of these, T790M was concurrently detected in three (50%) patients. HGF level was elevated in one patient with T790M mutation. Four patients underwent gefitinib plus PEM therapy, and five patients received treatment with gefitinib and S-1. The median number of cycles delivered was five, and the median progression-free survival was 5.8 months. Efficacy outcomes did not differ between the two treatment regimens. After the combination therapy, plasma T790M status changed to positive in two patients. HGF did not increase in any patient.

Conclusions: Data from noninvasive genetic profiling suggest that the retention of the T790M-positive cell population contributed to the better outcomes in response to combination therapy with EGFR-TKI and cytotoxic agents.

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