ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

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ABSTRACT

BACKGROUND

Patients with advanced midgut neuroendocrine tumors who have had disease progression during first-line somatostatin analogue therapy have limited therapeutic options. This randomized, controlled trial evaluated the efficacy and safety of lutetium-177 (^{177}Lu)–Dotatate in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors.

METHODS

We randomly assigned 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors to receive either ^{177}Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (^{177}Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol; a prespecified interim analysis of overall survival was conducted and is reported here.

RESULTS

At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001). In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group (P=0.004). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu-Dotatate group as compared with no patients in the control group, with no evidence of renal toxic effects during the observed time frame.

CONCLUSIONS

Treatment with ^{177}Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the ^{177}Lu-Dotatate group. (Funded by Advanced Accelerator Applications; NETTER-1 ClinicalTrials.gov number, NCT01578239; EudraCT number 2011-005049-11.)

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*A complete list of investigators in the Neuroendocrine Tumors Therapy (NETTER-1) trial is provided in the Supplementary Appendix, available at NEJM.org.

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