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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Neuroendocrine tumors of the midgut (which is defined as the jejunoileum and the proximal colon) commonly metastasize to the mesentery, peritoneum, and liver and are frequently associated with the carcinoid syndrome.[1,2] Neuroendocrine tumors of the midgut represent the most common type of malignant gastrointestinal neuroendocrine tumors and are associated with 5-year survival rates of less than 50% among persons with metastatic disease.[3,4] First-line systemic therapy usually consists of a somatostatin analogue for control of both hormonal secretion and tumor growth.[5-7] With the exception of everolimus for the treatment of nonfunctional neuroendocrine tumors,[8] no standard second-line systemic treatment options are currently available.[8,9]

Since 1992,[10-15] radiolabeled somatostatin analogue therapy (a form of treatment also known as peptide receptor radionuclide therapy) has shown considerable promise for the treatment of advanced, well-differentiated neuroendocrine tumors, a majority of which express high levels of somatostatin receptors to which somatostatin analogues bind.[16] This targeted form of systemic radiotherapy allows the delivery of radionuclides directly to tumor cells. Initial efficacy results were based on very high doses of ^{111}In-DTPA^{0}-octreotide,[11] but more promising results were subsequently found with ^{90}Y-DOTA^{0}-Tyr^{3}–octreotide (^{90}Y-DOTATOC)[17] and with ^{177}Lu-DOTA^{0}-Tyr^{3}–octreotate (^{177}Lu-Dotatate).[12] Lutetium-177 (^{177}Lu) is a beta- and gamma-emitting radionuclide with a maximum particle range of 2 mm and a half-life of 160 hours.[18] In a single-group trial of ^{177}Lu-Dotatate involving 310 patients who had gastroenteropancreatic neuroendocrine tumors, complete tumor remissions occurred in 2% of the patients and partial tumor remissions in 28%.[12] The median progression-free survival was 33 months.

We report here results from the phase 3 Neuroendocrine Tumors Therapy (NETTER-1) trial, which evaluated the efficacy and safety of ^{177}Lu-Dotatate as compared with high-dose octreotide long-acting repeatable (LAR) in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors.

METHODS

PATIENTS

This international, multicenter, phase 3 trial was conducted at 41 centers in 8 countries worldwide. Eligible patients were adults who had midgut neuroendocrine tumors that had metastasized or were locally advanced, that were inoperable, that were histologically confirmed and centrally verified, and that showed disease progression (according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1[19]) on either computed tomography (CT) or magnetic resonance imaging (MRI) over the course of a maximum period of 3 years during treatment with octreotide LAR (20 to 30 mg every 3 to 4 weeks for at least 12 weeks before randomization). Patients were required to have a Karnofsky performance-status score of at least 60 (on a scale from 0 to 100, with lower numbers indicating greater disability), a tumor with well-differentiated histologic features, and somatostatin receptors present on all target lesions (as confirmed by blinded, independent central review). Well-differentiated histologic features were defined as a Ki67 index (the percentage of cells that are positive for Ki67 as determined by immunostaining of the primary tumor) of 20% or less; tumors were assessed as low-grade if they had a Ki67 index of 0 to 2%, intermediate-grade if they had a Ki67 index of 3 to 20%, or high-grade if they had a Ki67 index of greater than 20%, with a lower grade indicating a lower rate of proliferative activity. Target lesions were selected from CT or MRI, and the degree of expression of somatostatin receptors was determined on the basis of the lesion that had the highest uptake of radiotracer observed on planar somatostatin receptor scintigraphy within 24 weeks before randomization. All CT and MRI images were reviewed and evaluated for disease progression (according to RECIST criteria) and somatostatin receptor expression by independent central reviewers who were unaware of the treatment assignments.

Key exclusion criteria were a serum creatinine level of more than 150 μmol per liter (1.7 mg per deciliter) or a creatinine clearance of less than 50 ml per minute; a hemoglobin level of less than 8.0 g per deciliter; a white-cell count of less than 2000 per cubic millimeter; a platelet count of less than 75,000 per cubic millimeter; a total bilirubin level of more than 3 times the upper limit of the normal range; a serum albumin level of more than 3.0 g per deciliter, unless the prothrombin time value was within the normal range; treatment with more than 30 mg of octreotide LAR within 12 weeks before randomization; peptide receptor radionuclide therapy at any time

before randomization; and any surgery, liver-directed transarterial therapy, or chemotherapy within 12 weeks before randomization.

TRIAL DESIGN

In this open-label, phase 3 trial, we randomly assigned patients, in a 1:1 ratio, to receive 177Lu-Dotatate plus best supportive care, consisting of octreotide LAR at a dose of 30 mg every 4 weeks for symptom control (177Lu-Dotatate group) or to receive high-dose octreotide LAR, at a dose of 60 mg every 4 weeks (control group). Randomization was performed with the use of a centralized permuted block (block size of 4) randomization scheme, with stratification according to the highest tumor uptake score on somatostatin receptor scintigraphy (grade 2, 3, or 4 on a scale ranging from 0 [no uptake by tumor] to 4 [very intense uptake by tumor] with higher grades indicating a higher level of expression of somatostatin receptors)[12] and according to the length of time that a patient had been receiving a constant dose of octreotide (≤6 months or >6 months).

In the 177Lu-Dotatate group, 7.4 GBq (200 mCi) of 177Lu-Dotatate was infused intravenously over a period of 30 minutes. Patients received four infusions every 8 weeks (cumulative radioactivity, 29.6 GBq [800 mCi]) unless unacceptable toxic effects occurred, centrally confirmed disease progression (according to RECIST) was present on imaging, the patient was unable or unwilling to adhere to trial procedures, the patient withdrew consent, or the patient died. For renal protection, an intravenous amino acid solution (Aminosyn II 10% [21.0 g of lysine and 20.4 g of arginine in 2 liters of solution] or VAMIN-18 [18 g of lysine and 22.6 g of arginine in 2 liters of solution]) was administered concomitantly for at least 4 hours, starting 30 minutes before infusion of the radiopharmaceutical. In the 177Lu-Dotatate group, patients continued to receive supportive care with octreotide LAR, which was administered intramuscularly at a dose of 30 mg approximately 24 hours after each infusion of 177Lu-Dotatate and then monthly after completion of all four treatments. In the control group, octreotide LAR at a dose of 60 mg was administered intramuscularly every 4 weeks. In both treatment groups, patients were allowed to receive subcutaneous rescue injections of octreotide in the event of hormonal symptoms (i.e., diarrhea or flushing) associated with their carcinoid syndrome.

TRIAL OVERSIGHT

This trial was sponsored by Advanced Accelerator Applications and was designed by Advanced Accelerator Applications in collaboration with the last two authors. The trial protocol was approved by the investigational review board or independent ethics committee at each participating institution. Contract research organizations monitored the trial and collected, compiled, maintained, and analyzed the data. The trial was performed in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable regulations. All the patients provided written informed consent. An independent data and safety monitoring board oversaw the conduct of the trial. The first draft of the manuscript was prepared by the first author with assistance from a professional medical writer funded by the sponsor. All the authors contributed to subsequent drafts and agreed to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and the analysis and for the fidelity of the trial to the protocol. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to documented disease progression (as evaluated by independent central review by radiologists who were unaware of the treatment assignments) or death from any cause. Secondary end points included the objective response rate, overall survival (defined as the time from randomization to death from any cause), safety, and the side-effect profile. An objective tumor assessment on CT or MRI was performed every 12 weeks after the date of randomization in both treatment groups. The treatment was considered to have failed if a patient had progressive disease on imaging, according to central assessment with the use of RECIST criteria, and patients with treatment failure proceeded directly to the long-term follow-up phase. We calculated the response rate as the percentage of patients who had a response according to RECIST (sum of partial responses and complete responses). Definitions of all response categories are provided in the protocol.

Safety was assessed (at least every 2 to 12 weeks, depending on the phase of the trial [treatment phase or follow-up phase] and treatment group)

on the basis of adverse events (which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03), laboratory results (hematologic, chemical, and urologic), physical examinations, vital signs, electrocardiography, and Karnofsky performance status. Additional details are provided in the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

We calculated the required number of patients for the trial assuming that the median progression-free survival would be 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group, the study would have 90% nominal power at an alpha level of 5%, and the prespecified enrollment period and follow-up period for both groups would be 18 months. On the basis of those assumptions, we calculated that we needed a sample of 124 patients, and the analysis of the primary end point was planned to be conducted after at least 74 events of disease progression or death that were centrally confirmed and could be evaluated had occurred. However, the sample size of the trial was adjusted to 230 patients to enable us to detect a statistically significant and clinically relevant difference between the two treatment groups in overall survival as a secondary end point. This calculation was based on the assumption that the median overall survival would be 50 months in the ^{177}Lu-Dotatate group and 32 months in the control group, with 80% nominal power at an alpha level of 5%, and a prespecified enrollment period of 18 months and a long-term follow-up period of 60 months. A prespecified interim analysis of overall survival was conducted at the time of the analysis of progression-free survival. The final analysis of overall survival is planned to be performed either after 158 deaths have occurred or 5 years after the last patient underwent randomization, whichever occurs first.

All patients who underwent randomization were included in the analyses of efficacy, demographics, and baseline characteristics. The safety population, which comprised all patients who underwent randomization and received at least one dose of trial treatment, was used for all safety analyses. The median point estimate and 95% confidence interval for progression-free survival and overall survival were estimated by means of the Kaplan–Meier method. Objective response rates and corresponding 95% confidence intervals were calculated for each treatment group and were compared with the use of Fisher's exact test. Survival curves were compared with the use of an unstratified log-rank test and were tested against the null hypothesis. Hazard ratios were estimated with the use of an unstratified Cox proportional-hazards model.

RESULTS

PATIENTS

From September 2012 through mid-January 2016, a total of 229 patients underwent randomization at 41 sites (27 sites in Europe and 14 in the United States); 221 of the 229 patients who underwent randomization received at least one dose of trial treatment, including 111 patients in the ^{177}Lu-Dotatate group and 110 in the control group (safety population) (Fig. S1 in the Supplementary Appendix). The demographic and clinical characteristics of the patients were well balanced between the two treatment groups; the ileum was the primary tumor site in a majority of patients (73%), and most patients presented with metastases in the liver (83%), the lymph nodes (62%), or both, typically in the mesentery or retroperitoneum (Table 1, and Table S1 in the Supplementary Appendix). The treatment groups were well balanced with respect to tumor grade (low-grade [grade 1] Ki67 proliferation index in 66% of patients in the ^{177}Lu-Dotatate group and in 72% in the control group) and with respect to the highest uptake of tumor somatostatin radiotracer (high-grade [grade 4] uptake in 61% of patients in the ^{177}Lu-Dotatate group and in 59% of patients in the control group). Serum chromogranin A levels and 5-hydroxyindoleacetic acid levels in a 24-hour urine specimen were similar in the two treatment groups. Approximately 80% of the patients had undergone previous surgical resection (78% in the ^{177}Lu-Dotatate group and 82% in the control group), and nearly half the patients had undergone a previous form of systemic therapy other than somatostatin analogue therapy (41% of patients in the ^{177}Lu-Dotatate group and 45% in the control group).

EFFICACY

At the time of the data cutoff for the primary analysis (July 24, 2015), 23 events of disease

Table 1. Demographic and Baseline Clinical Characteristics of All Patients Who Underwent Randomization.*

Characteristic	177Lu-Dotatate Group (N=116)	Control Group (N=113)
Sex — no. (%)		
Male	63 (54)	53 (47)
Female	53 (46)	60 (53)
Age — yr	63±9	64±10
Body-mass index†	25±5	26±7
Median time since diagnosis — yr	3.8	4.8
Primary tumor site — no. (%)		
Ileum	86 (74)	82 (73)
Small intestine, not otherwise specified	11 (9)	12 (11)
Midgut, not otherwise specified	9 (8)	7 (6)
Jejunum	6 (5)	9 (8)
Right colon	3 (3)	1 (1)
Appendix	1 (1)	2 (2)
Site of metastasis — no. (%)		
Liver	97 (84)	94 (83)
Lymph nodes	77 (66)	65 (58)
Mesentery	17 (15)	8 (7)
Bone	13 (11)	12 (11)
Other	15 (13)	10 (9)
Peritoneum	7 (6)	10 (9)
Lungs	11 (9)	5 (4)
Ovaries	1 (1)	9 (8)
Somatostatin receptor scintigraphy, Krenning scale — no. (%)‡		
Grade 2	11 (9)	12 (11)
Grade 3	34 (29)	34 (30)
Grade 4	71 (61)	67 (59)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The Krenning scale ranges from grade 0 (no uptake by tumor) to grade 4 (very intense uptake by tumor), with higher grades indicating a higher level of expression of somatostatin receptors. The highest grade per patient was reported.

progression or death had occurred in the 177Lu-Dotatate group and 68 such events had occurred in the control group. The estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the 177Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median progression-free survival had not yet been reached in the 177Lu-Dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with 177Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; P<0.001), which represented a 79% lower risk of disease progression or death in the 177Lu-Dotatate group than in the control group (Fig. 1A). Consistent treatment benefits associated with 177Lu-Dotatate were observed irrespective of stratification factors and prognostic factors, which included levels of radiotracer uptake on somatostatin receptor scintigraphy, tumor grade, age, sex, and tumor marker levels (Fig. 1C).

In addition to the analysis of progression-free survival, we performed a planned interim analysis of overall survival. A total of 14 deaths in the

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