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Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival

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Key Words
Octreotide LAR · Somatostatin analogs · Neuroendocrine tumors · Midgut · Overall survival

Abstract
Background: Somatostatin analogs have been shown to control the growth of well-differentiated metastatic neuroendocrine tumors. Their effect on overall survival is a matter of debate. We analyzed the prognostic significance of early treatment with octreotide LAR and of hepatic tumor load in the PROMID trial cohort. ***Patients and Methods:*** Between 2001 and 2008, 85 treatment-naïve patients were randomly assigned to monthly octreotide LAR 30 mg or placebo until tumor progression or death. Post-study treatment was at the discretion of the investigator. Upon disease progression, 38 out of 43 placebo patients (88.4%) received octreotide LAR. For survival, patients were followed until May 2014. ***Results:*** Forty-eight out of 85 patients (56.5%) died. In 38 patients (79.2%), death was tumor related. The median overall survival (84.7 and 83.7 months) was only slightly different in patients assigned to octreotide and placebo [HR = 0.83 (95% CI: 0.47–1.46); p = 0.51]. The median overall survival was 84.7 months for all 85 patients, 107.6 months in the low-tumor-load (n = 64) and 57.5 months in the high-tumor-load (n = 21) subgroups [HR = 2.49 (95% CI: 1.36–4.55); p = 0.002]. There was a trend towards improved overall survival in patients with a low hepatic tumor load receiving octreotide compared to placebo ['median not reached' and 87.2 months; HR = 0.59 (95% CI: 0.29–1.2); p = 0.142]. ***Conclusion:*** The extent of tumor burden is a predictor for shorter survival. Overall survival was similar in patients receiving octreotide LAR or placebo treatment at randomization. Crossover of the majority of placebo patients to octreotide LAR may have confounded the data on overall survival.

The preliminary results of this study have been partly presented at the ASCO annual meeting in 2013 [J Clin Oncol 2013;31(suppl):abstract 4030].

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Introduction

Long-acting somatostatin analogs compared to placebo significantly lengthened time-to-tumor progression (TTP) in patients with metastatic well-differentiated, mostly G1, midgut neuroendocrine tumors (NET; octreotide LAR: PROMID study [1]). Progression-free survival (PFS) was also improved in patients with advanced, nonfunctioning enteropancreatic NETs of grade 1 or 2 and documented disease-progression status (lanreotide autogel: CLARINET study [2]). Whether or not the beneficial effect on TTP and PFS demonstrated in both trials favorably affects overall survival has not been investigated so far.

Lengthening of TTP or PFS observed during treatment with somatostatin analogs could be surrogate markers for improved overall survival. Longer survival durations have been shown in NET patients who were diagnosed from 1988 to 2004 compared to survival durations in NET patients who were diagnosed from 1973 to 1987 [3]. The somatostatin analog octreotide was the only new drug introduced to treat NETs during the period after 1987. In addition, a survival advantage has been shown for patients responding to treatment with biotherapy compared to those who did not respond [4]. Only properly designed, controlled and prospective studies can prove this important question.

The aim of this long-term follow-up study was to analyze the prognostic significance of early treatment with the somatostatin analog octreotide LAR versus treatment with placebo for overall survival in patients included into the PROMID trial. The hypothesis was that patients with metastatic midgut NETs live longer if treated immediately after randomization than patients in the placebo arm who received treatment only after documented tumor progression. In addition, we wanted to investigate the prognostic impact of the extent of hepatic tumor load on overall survival.

Patients and Methods

Patients

Details of the PROMID study design and the patient characteristics have been described earlier [1]. In short: between July 2001 and January 2008, 42 and 43 patients with locally inoperable or metastatic NET (midgut primary tumor or unknown origin believed to be of midgut origin; proof of a well-differentiated histology by pathology) have been randomly assigned to receive 30 mg octreotide LAR (Sandostatin® LAR; Novartis, Nuremberg, Germany) or placebo. Most patients (85.9%) had metastatic spread to the liver, and 64 out of 85 patients had low (≤10%) liver involvement. Hepatic tumor load was determined by a single expert radiologist from four to six slices of a CT/MRI scan by a semiquantitative three-dimensional approach and categorized into five groups. Replacement of not more than 10% of the liver by metastases was defined as low tumor load, whereas a replacement exceeding 10% was defined as high tumor load [4]. The primary end point was TTP calculated from the date of randomization until the date of first progressive disease or tumor-related death. This multicenter work was a double-blind, prospective and randomized study, and its results have been published recently [1]. According to the original study protocol, analysis of the time to tumor-related death should be based on 121 events. Because of the observed positive effects of octreotide LAR on tumor growth found in the published interim analysis on 85 patients [1] and a low recruitment rate, stop of further enrollment and a follow-up of the study population on a yearly basis until death was decided in 2008.

Patients were followed until May 2014. Post-study treatment was at the discretion of the local investigators. They invited the patients to present in person at the center and sent information on the actual performance status and treatment to the Center for Clinical Trials in Marburg. In case the patient had died, the investigators contacted the patient's family doctors by telephone and asked for a written document on the post-study treatment and cause of death. Overall survival was calculated twice: as the time from diagnosis to death and as the time from random assignment to death.

Statistical Analysis

Overall survival, the second primary end point, was analyzed using the Kaplan-Meier method. Treatment groups (octreotide LAR vs. placebo) and hepatic tumor load at study entry (≤10 vs. >10%) were compared using the log-rank test, and hazard ratios were estimated (point estimates and 95% CIs) using the Cox proportional hazard model with or without stratification. The significance level for two-sided statistical testing differences between the treatment groups was 0.05. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, N.C., USA).

A total of 121 observed tumor-related deaths for the analysis of survival time were initially planned for detection of a hazard ratio of 0.6 with a power of 80%. On the basis of 48 observed deaths and 38 observed tumor-related deaths, the power was reduced to 42% for overall survival and 35% for tumor-related death, or a stronger effect size of a hazard ratio of 0.45 and 0.40, respectively, was needed to keep with the power of 80%.

Results

Post-Study Treatment

The first primary end point of the PROMID study was TTP or tumor-related death [1]. After documented tumor progression, treatment was at the discretion of the center participating in the study. All patients of the placebo group (n = 43) developed progression (n = 41) or died (n = 2) during the PROMID core study, whereas 4 out of 42 patients of the octreotide arm were still without progression at the last evaluation during the follow-up study. Post-study treatment in patients randomly as-

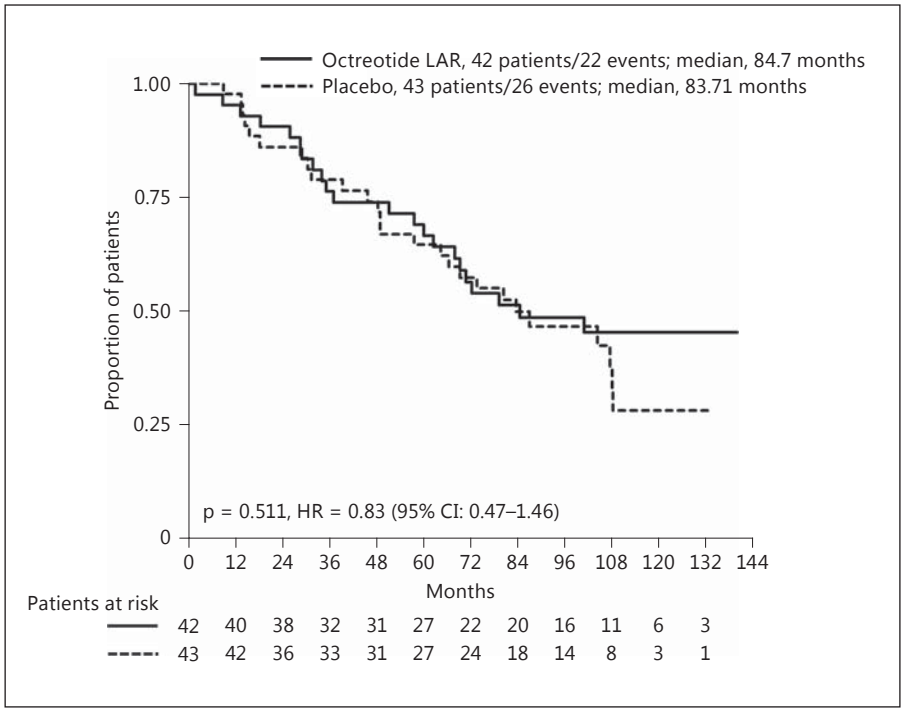

Fig. 1. Overall survival in the whole cohort of 85 patients included into the PROMID study according to treatment (conservative intention-to-treat analysis).

signed at registration to octreotide LAR and placebo included octreotide LAR (29 vs. 38 patients), hepatic (chemo-)embolization (5 vs. 12 patients), peptide receptor radiotherapy (PRRT; 14 vs. 13 patients) and chemotherapy (4 vs. 5 patients). The median duration of octreotide LAR treatment from randomization until the last evaluation was 70.5 months (range 1.2–140.2) in the octreotide group and 53.1 months (range 0.1–127) from the start of octreotide LAR due to progression in the placebo arm until the last evaluation. The median time between randomization and the first injection of octreotide in the 38 patients of the placebo arm was 9.2 months (range 2–82).

Death Rates and Causes of Death

After randomization, the patients were followed until May 2014 (longest follow-up 144 months; median follow-up: 96 months). Forty-eight out of 85 patients (56.5%) died. In 38 out of 48 patients (79%), death was the consequence of the NET disease; in 2 patients (4.2%), it was related to second malignancies (leukemia, bladder cancer) and in 8 patients (16.7%), it was not tumor related (table 1). At that time, the death rates in patients randomly assigned to receive octreotide LAR and placebo were 52.4 and 60.5%, respectively, not being significantly different (table 1). Causes of not tumor-related death included myocardial infarction, septic shock and stroke.

Table 1. Causes of death in the 85 patients included into the PROMID study

	Octreotide LAR (n = 42)		Placebo (n = 43)		Total (n = 85)	
	n	%	n	%	n	%
NET related	17	40.5	21	48.8	38	44.7
Related to other malignancy	1	2.3	1	2.3	2	2.3
Not tumor related	4	9.5	4	9.3	8	9.4
Total	22	52.4	26	60.5	48	56.5

Forty-two patients were randomized to receive octreotide LAR and 43 patients to receive placebo until documented tumor progression. After documented tumor progression in both study arms, the treatment was at the discretion of the center participating in the PROMID study. Patients were followed up until May 2014.

The median overall survival from randomization for all 85 patients was 84.7 months, 84.7 months in the subgroup of patients assigned to receive octreotide LAR and 83.7 months in the subgroup assigned to receive placebo [HR = 0.83 (95% CI: 0.47–1.46); p = 0.51] (fig. 1). The calculated 5- and 10-year survival rates from the date of randomization were 66.5 and 45.3%, respectively. The

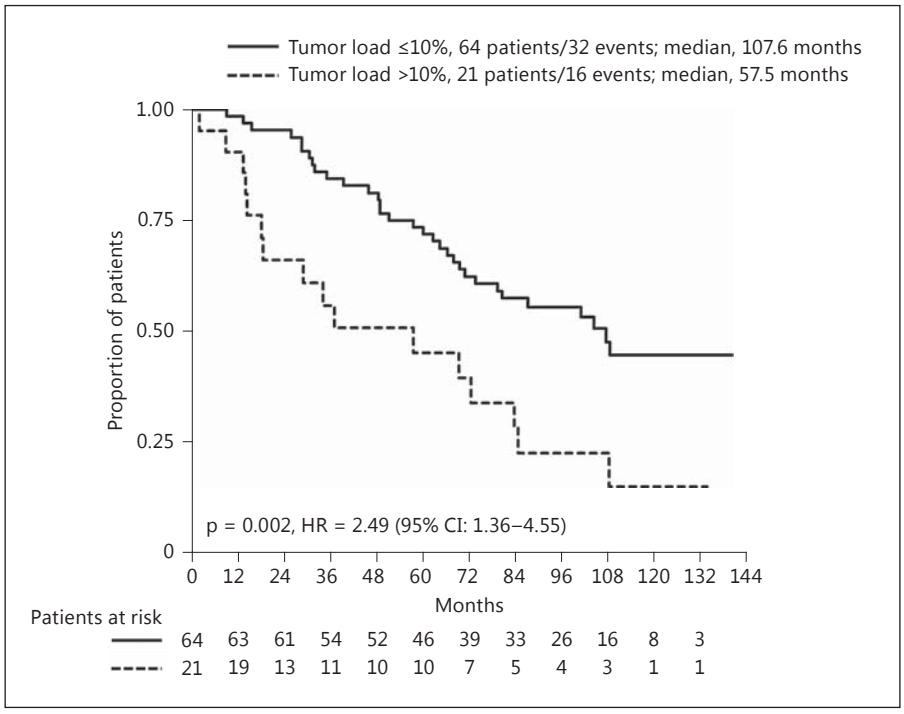

Fig. 2. Overall survival in the whole cohort of 85 patients included into the PROMID study according to hepatic tumor load (conservative intention-to-treat analysis).

Table 2. Number of deaths according to hepatic tumor load

	Octreotide LAR (n = 42)		Placebo (n = 43)		Total (n = 85)	
	n	%	n	%	n	%
Total	22	52.4	26	60.5	48	56.5
HL ≤10%	13 of 32	40.6	19 of 32	59.4	32 of 64	50.0
HL >10%	9 of 10	90.0	7 of 11	63.6	16 of 21	76.2

HL = Hepatic tumor load.

median overall survival from the date of diagnosis was 106 months, and the calculated 5- and 10-year survival rates were 76.2 and 46.8%, respectively. The results for overall survival to tumor-related death were similar [HR = 0.78 (95% CI: 0.41–1.49)].

Death in the Subgroups

The death rates depended on hepatic tumor burden at randomization. Thirty-two out of 64 patients (50.0%) with a hepatic tumor load ≤10% and 16 out of 21 patients (76.2%) with a hepatic tumor load >10% died (table 2).

The median overall survival of patients in the high-hepatic-tumor-load (>10%) subgroup was 57.5 months and considerably shorter in comparison to the 107.6 months in the low-hepatic-tumor-load (≤10%) subgroup [HR = 2.49 (95% CI: 1.36–4.55); p = 0.002] (fig. 2).

There was a trend for improved overall survival in patients with a limited hepatic tumor load (≤10%) receiving octreotide LAR at randomization compared to the placebo group. The median overall survival was 'not reached' in the octreotide LAR and 87.2 months in the placebo group [HR = 0.59 (95% CI: 0.29–1.20); p = 0.142] (fig. 3). In this subgroup, the median overall survival from diagnosis to tumor-related death was 'not reached' in the octreotide LAR and 107.6 months in the placebo group [HR = 0.50 (95% CI: 0.22–1.16); p = 0.11].

Overall survival was not dependent on the presence or absence of carcinoid syndrome [HR = 0.945 (95% CI:

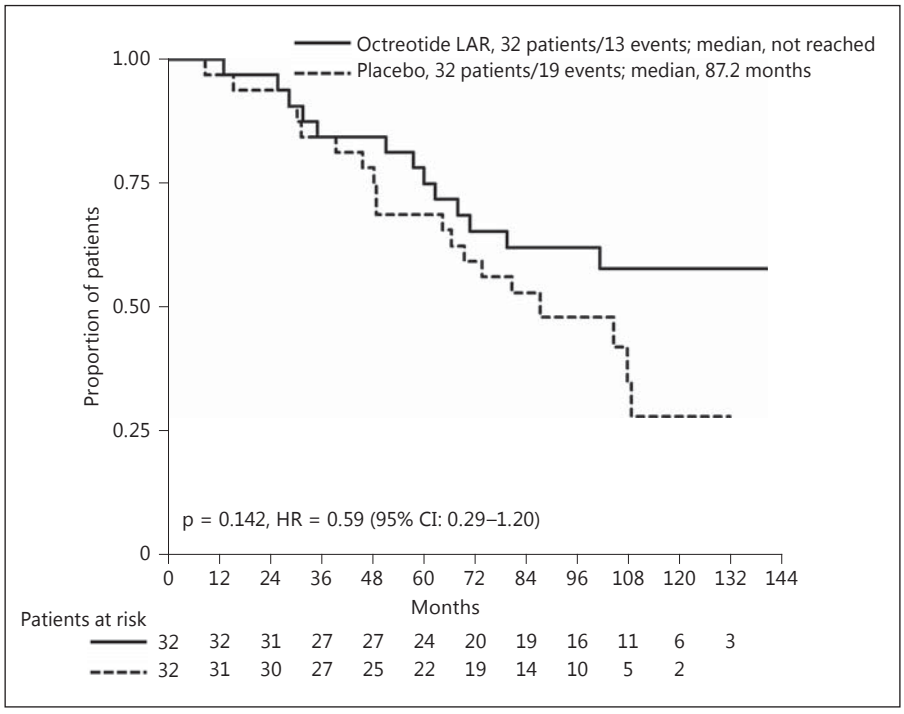

Fig. 3. Overall survival in the subgroup of 64 patients with a hepatic tumor load ≤10% according to treatment (conservative intention-to-treat analysis).

0.53–1.70); p = 0.85]. In contrast, overall survival was longer in patients who had been submitted to primary tumor resection [HR = 0.39 (108 vs. 49 months; 95% CI: 0.22–0.69); p = 0.0011]. The rate of primary tumor resection was well balanced between the treatment arms; stratification according to primary tumor resection did not change the results regarding treatment effects.

Discussion

This follow-up study provides for the first time long-term survival data on a well-characterized study population: only treatment-naïve patients with metastatic disease, mostly G1 midgut NETs, were included into the PROMID trial [1]. The median overall survival from diagnosis and randomization was 106 and 84.7 months, respectively. The calculated 5- and 10-year survival rates from randomization were 67 and 45%, respectively. The study confirms the finding of previous reports that tumor burden is a strong predictor of outcome [3, 5–9]. Our analysis was based on 48 deaths in the whole study group of 85 patients (56.5%). Thirty-two deaths occurred in 64 patients of the subgroup with a low hepatic tumor load (50.0%) and 16 deaths occurred in 21 patients of the subgroup with a high hepatic tumor load (76.2%). Overall survival was considerably longer in patients with a hepatic tumor load ≤10% at randomization (median overall survival: 106 months) compared to patients in the subgroup with a higher hepatic tumor load (median overall survival: 58 months). Although not available for all patients, CT/MRI scans during follow-up indicated that a low tumor burden at randomization later switched to a higher tumor load in deceased patients. These results suggest that all patients with metastatic disease should be carefully followed. We observed a longer overall survival in the subgroup of patients with resection of the primary tumor prior to the core study, corresponding to longer TTP in this subgroup.

Treatment with octreotide LAR significantly lengthened TTP as compared to placebo treatment in patients with metastatic midgut NETs included into the PROMID trial [1]. Analysis of the follow-up data could not prove that this effect on tumor progression translates in a statistically significant increase in the overall survival. However, all patients in the initial placebo group received active treatment upon tumor progression, which in most patients (38 out of 43) consisted of octreotide LAR, and in case of further progression of PRRT, hepatic (chemo-) embolization and chemotherapy. Whereas the percentage of patients treated with PRRT and chemotherapy was similar in both groups, the percentage of patients treated

with liver-directed therapies was higher in the placebo group compared with the octreotide group. It is unclear how these treatments influenced overall survival.

In the overall survival analysis of patients with a low hepatic tumor load, we found an estimated HR of 0.59 in the octreotide LAR-treated group compared to patients treated with placebo. This could indicate a statistically not proven ($p = 0.14$) risk reduction of 41% in favor of octreotide LAR. However, the small number of events (32 out of 64) observed so far does not permit a definitive conclusion. The effect of octreotide LAR on overall survival may have been confounded by the crossover to octreotide LAR treatment after tumor progression in the majority of patients originally randomized to placebo at study entry.

Comparison of our prospectively collected survival data with results from published, almost exclusively retrospective studies shows considerable differences. For patients included in the PROMID trial, the median overall survival from the date of diagnosis was 106 months, and the corresponding 5- and 10-year survival rates were 76 and 46%, respectively.

Using the SEER database [3], the median survival duration in 35,097 NET cases was 75 months. In patients with distant disease and well- or moderately differentiated tumors, the median overall survival was only 33 months. The PROMID cohort consisted of patients with confirmed or suspected intestinal primaries, and the majority had liver metastases. The median survival in the subgroup of jejunal and ileal tumors of the SEER registry was 88 months and only 56 months if distant metastases were present [3]. The survival data of our study cohort compare favorably with these population-based data. For the patients entered in the PROMID trial, we could show that the extent of tumor burden is a strong predictor of survival. Patients with a high liver tumor burden had an overall survival from randomization of 57 months as compared to 107 months for patients with a low tumor burden.

A retrospective single-center study from Germany that included 249 patients with midgut and 21 patients with hindgut NETs reported 5- and 10-year survival rates of 83 and 59%, respectively, in stage IV patients [9]. In the Spanish tumor registry, the 5-year survival rate of 80 patients with stage IV NETs arising in the jejunum/ileum was 82% [10]. Recently, survival data from 691 patients with jejunal and ileocecal NETs treated at the Moffitt Cancer Center, Tampa, Fl., USA, between 2000 and 2010 have been provided [11]. The 5-year overall survival rate for stage IV patients was 72%. In the retrospective UKINETS study on 360 patients with midgut NETs metastatic to the liver, median survival from the date of diagnosis was 92 months, and the 5-year survival was 66% [12]. These center-based data are comparable to the prospective data from the PROMID trial, with an overall survival starting from the time of diagnosis of 106 months and a 5-year survival of 76%.

Even data from different prospective trials are difficult to compare, as shown for patients included into the PROMID trial and the recently published CLARINET trial. The PROMID cohort was randomized without an observation period prior to randomization; therefore, spontaneous tumor growth was unknown. For ethical reasons, the investigators decided to avoid randomization of patients with documented tumor progression to placebo treatment. In the CLARINET trial, patients with metastasized gastroenteropancreatic NETs and a Ki-67 proliferation index <10% were randomized to lanreotide autogel or placebo. Ninety-six percent of the patients had stable disease according to RECIST in the 3–6 months before randomization. In contrast, 50% of the patients included in the PROMID trial and randomized to receive placebo were progressive after 6 months [1]. TTP in the PROMID study was 14.3 months for the octreotide and 6.0 months for the placebo group. The respective figures for PFS of the midgut subgroup in the CLARINET study were much longer: 'not reached' in the lanreotide and 21 months in the placebo group [2]. Both trials reach identical conclusions concerning the key message: long-acting somatostatin analogs inhibit tumor growth and prolong TTP and PFS. However, the trials markedly differ with respect to the underlying absolute figures for TTP and PFS. The use of different response criteria (the bidimensional WHO criteria vs. the unidimensional RECIST) and the inclusion of patients with different tumor biology, especially the selection of patients without disease progression before randomization into the CLARINET trial, may contribute to the obvious differences found in both trials. In future studies, tumor growth behavior at study entry should be documented.

To conclude, this prospectively designed study provides for the first time long-term survival data for patients with metastatic midgut NETs. The study shows that a high tumor burden is a strong indicator for a shorter survival. Patients with a low tumor burden displayed a favorable prognosis with a median survival of 107 months after randomization. There was a tendency for a survival advantage in the group of patients with a low hepatic tumor load at the time of randomization, which was not observed for the whole cohort of patients treated with octreotide LAR.

Overall, despite the limitations of our long-term follow-up study discussed above, it appears that in asymptomatic patients with well-differentiated midgut NETs, a watch-and-wait strategy, delaying treatment with active compounds such as long-acting somatostatin analogs until tumor progression offers no significant survival disadvantage over an early start of treatment. Individualized treatment recommendations taking into account risk factors for tumor progression, such as the proliferation rate and tumor load as well as the patient's wish, are warranted.

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Disclosure Statement

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