Tumor growth rate in intestinal/pancreatic neuroendocrine tumors: post hoc exploratory analysis of data from the CLARINET study

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Background

• The slow growing nature of neuroendocrine tumors (NETs) can confound accurate and early assessment of disease status with the widely used response evaluation criteria in solid tumors (RECIST).1,2
• New objective measures of tumor response that detect subtle changes in tumor growth or stabilization over a shorter treatment period are needed to complement RECIST.

• Tumor growth rate (TGR) is one promising candidate.

• The CLARINET study demonstrated anti-tumor efficacy of lanreotide depot (also known as autogel) in patients with intestinal and pancreatic NETs.3–5
• Centrally assessed tumor measurements (based on RECIST vs.0) were used to determine radiologic progression.

• In these post hoc analyses, tumor measurements from CLARINET were re-evaluated to explore the clinical utility of TGR as:
  – Measure of tumor progression before and in response to treatment.
  – Prognostic factor for tumor progression before treatment.

Methods

Overview of CLARINET

• CLARINET was an international randomized double-blind placebo-controlled phase 3 study (BudR-CET; 2005-004094-35; ClinicalTrials.gov
  – NCT00535362).

• Patients received lanreotide depot 120 mg or placebo every 28 days for 96 weeks or until death or progressive disease (PD; assessed centrally using RECIST vs.0).

• Study visits were scheduled during screening and at weeks 1, baseline, 12, 24, 36, 48, 72, and 96.

• A computed tomography (CT) scan was performed twice during screening to determine pre-treatment disease progression status. Single CT scans were obtained thereafter.

Assessments and analyses

• TGR was expressed as the percentage change in tumor volume over 1 month:
  \[
  \text{TGR} = 3 \times \log \left( \frac{D_2}{D_1} \right)
  \]

– As a prognostic factor (post hoc analyses; ITT population):

  • TGR was used to determine the optimum pre-treatment TGR cut-off (%/month) for predicting the risk of progression.
  • Kaplan-Meier plots were used to describe PFS based on pre-treatment TGR.
  • Hazard ratios (HRs) were estimated from Cox regression models.

• Additional prognostic factors for PFS were estimated from Cox regression models.

Statistical analyses

• TGRs prior to and in response to treatment (post hoc analyses; intention-to-treat [ITT] population):

  • Least square (LS) means (95% confidence intervals, CI) were estimated using mixed-model regression models.

  • Pairwise comparisons using the Wilcoxon signed-rank test were performed to test differences in TGR means during treatment.

TGR to measure tumor progression

• Although 77% (95) of evaluable patients had stable disease (SD) before treatment according to RECIST vs.0, TGR analyses showed that a large proportion of tumors were growing (Figure 1).

• A reduction in TGR after only 12 weeks with lanreotide depot vs. placebo, resulted in a significant difference between treatment groups that was maintained throughout the treatment period (Figure 2).

TGR as a prognostic factor

• Of the pre-treatment TGR thresholds assessed by ROC analysis, a value of 4%/month was optimal for predicting the risk of progression independently of treatment group.

  • Pre-treatment TGR >4%/month had a 4.1-fold greater risk of progression than TGR ≤4%/month in the overall population (HR = 4 [95% CI: 2.6, 6.5]; p<0.001, n=187).

Results

Baseline characteristics

• A total of 204 patients were randomized (ITT population) to lanreotide depot (n=101) or placebo (n=103).

• Of these, 66% (144) had grade 1 tumors (G1-2), <20%, 30% (60) had grade 2 tumors (G2-3), >20%, 37% (73) had hepatic tumor loads >25%, >45% (91) had primary tumors of the pancreas and >36% (73) of the midgut.

• A total of 200 evaluable patients with SD measurements were included in these post hoc analyses, unless otherwise stated.

• TGR was used to determine radiologic progression.

Limitations

• This is a post hoc analysis, albeit from a large homogenous study population.

• Target lesions were assumed to be spherical, which tends to be the case for liver metastases.

Conclusions

• Compared with RECIST, TGRs provided more precise and rapid information on tumor kinetics before treatment, revealing anti-tumor effects of lanreotide depot/autogel as early as 12 weeks.

• Pre-treatment TGR (regressor of treatment) was a prognostic factor for later PFS outcomes. Lanreotide was more effective than placebo in delaying progression, irrespective of pre-treatment TGR.

• These findings suggest TGR has potential clinical utility as a novel outcome measure for tumor progression.

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References

5. CLARINET Study Group

Figure 1. Distribution of TGRs among individual patients during the screening period according to RECIST classification.

Figure 2. Estimated LS means TGRs calculated between consecutive visits.

Figure 3. Kaplan-Meier plot of PFS in patient with TGRs (a) <4%/month and (b) >4%/month during the pre-treatment period.

*Pre-treatment TGR is calculated from the screening scan and baseline scan (week 1). CI, confidence interval; LS, least square means; PFS, progression-free survival; TGR, tumor growth rate.