Serum neuron-specific enolase level is an independent predictor of overall survival in patients with gastroenteropancreatic neuroendocrine tumors

Serum neuron-specific enolase (NSE) is considered a tumor marker in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [1]. It is elevated in 30%–50% of GEP-NET patients and correlates with tumor size [2, 3]. NSE has a sensitivity of 38% and specificity of 73% for GEP-NET detection [2]. The prognostic role of serum NSE as a biomarker for GEP-NETs’ patients’ survival is poorly studied [4].

We retrospectively studied 592 patients with sporadic (nonfamilial) ENETS TNM stage IV GEP-NETs. Median follow-up was 58.7 months (25th–75th percentile: 34.02–92.98). Serum NSE was measured at first consultation, using enzyme immunoassay (NSE Cobas E602, Roche Diagnostics, Mannheim, Germany). Cutoff values for serum NSE were: NSE ≤1× ULN (≤16.2 µg/l), NSE 1–3× ULN (16.2–48.6 µg/l) and NSE >3× ULN (48.6 µg/l).

Primary outcome was overall survival, calculated from date of diagnosis to date of death by any cause, or date of last follow-up. Using statistical software R version 3.1.3 ‘survival’ package, overall survival was estimated with the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportional hazards models including age at diagnosis, OctreoScan® (SRS) positivity (Krenning Scale estimated with Cox proportional hazards models including age 1.96 (1.45–2.63), primary tumor site, sex and bone metastases.

Two hundred forty-two (41%) of GEP-NET patients had an elevated NSE (≥1× ULN). NSE >3× ULN were seen in pancreatic NETs.

Median overall survival (mOS) across all groups was 103.9 months (95% CI 92.8–137.1). mOS was 161.8 months in the NSE ≤1× ULN group [95% CI 130.7–not reached (NR)] and 72.5 months in the NSE 1–3× ULN group [95% CI 60.2–108.6; Cox proportional hazard-adjusted HR versus NSE ≤1× ULN: 1.96 (1.45–2.63), P < 0.001]. In the NSE >3× ULN group, mOS was 27.8 months [95% CI 15.2–44.7; HR versus NSE ≤1× ULN: 6.15 (4.36–8.69), P < 0.001] (Figure 1). Significant contributors to our model included: age at diagnosis [HR 1.03 (1.02–1.04), P < 0.001] and SRS positivity [HR 0.48 (0.28–0.83), P < 0.001].

The ENETS/WHO grading system using Ki-67 staining was introduced in 2010 [5]. Therefore, we used SRS positivity as a surrogate marker for ENETS/WHO tumor grading, since SRS-positive GEP-NETs are generally well-differentiated, ENETS/WHO grade 1–2 tumors. However, the assumption that all SRS positive patients could have ENETS/WHO grade 1–2 tumors could be considered a limitation of this study. We therefore studied the subpopulation of 367 patients with known ENETS/WHO 2010 grading (62% of all patients). In this population, the same Cox proportional hazard model with ENETS/WHO grade as an additional parameter was applied and showed that higher

ENETS/WHO grade significantly contributed (P < 0.001) to the model, but that NSE remained independently associated with overall survival (P < 0.001). Multivariate analysis data are shown (supplementary Table S1, available at Annals of Oncology online).

This study demonstrates that NSE is a biomarker for overall survival in ENETS TNM stage IV GEP-NET patients. Our study cohort had a median follow-up of almost 5 years and an mOS of over 8.5 years across all groups. Elevated NSE was found in over 40% of patients, confirming published data [2, 3]. Elevated serum NSE indicates a more aggressive disease course and determination of NSE at first consultation could, therefore, have prognostic implications.

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**disclosure**

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The recently published cost-effectiveness analysis by Goldstein et al. [5] emphasizes the high incremental cost with low incremental benefit of regorafenib in mCRC. It is an additional example of a novel anticancer drug that provides low value at its current cost and another major challenge for finding new ways of pricing and payment systems [6]. In addition to current strategies, we would suggest to consider NNT for developing a new pricing/reimbursement strategy for novel biologic agents [7]. The NNT offers a measurement of the impact of a medicine or therapy by estimating the number of patients that need to be treated to prevent one additional adverse outcome. For trials with a binary outcome, the NNT can be obtained as the reciprocal of the absolute difference in proportions of patients with the outcome of interest. In trials using a time-to-event end point, the NNT can be calculated in a similar way, as the reciprocal of the difference between survival probabilities in the active and control treatment groups at a chosen time point. Having the HR and the survival rates, the NNT will be calculated as: NNT = 1/[Sc(t)HR – Sc(t)] where Sc(t) is the survival for control group at time ‘t’. NNTs can be rounded up to the nearest whole number and accompanied by the 95% CI. For example, with an HR = 0.8 and a survival rate of 60% in the control group at 12 months, the NNT will be 1/(0.6×0.8–0.6) ≈16 patients [7]. Therefore, 16 patients have to be treated with the experimental drug for one additional patient to survive at that time point.

We evaluated survival data and OS curves reported in the CORRECT trial publication [4], and we estimated a 10.9 NNT and a 10.4 NNT at 6 and 9 months, respectively (Table 1). The observed 6.4 months median OS in the regorafenib group falls between these two time points. As provided in Table 1, on average 10 patients (95% CI 6–44) are needed to be treated with regorafenib to prevent one additional event (death) compared with placebo. The more recent phase III CONCUR trial of regorafenib monotherapy was conducted in Asia and in a less heavily pretreated patient population [8]. The median OS (primary end point) was 8.8 months with regorafenib versus 6.3 months with placebo (HR 0.55; 95% CI 0.40–0.77). As presented in Table 1, the NNT in the CONCUR trial at 9 months is 4.6 (95% CI 3–10). Accordingly, on average 5 patients are needed to be treated with regorafenib to prevent one additional event (death) compared with placebo.

Payment of regorafenib for treating mCRC patients in third-line setting could be negotiated according to the results of the NNT analysis. Assuming the use of regorafenib in Western countries and in patients resembling the CORRECT study population, the negotiation between the pharmaceutical company and a national health care system could be based on cost reductions between 1/6 (lower limit of the 95% CI of the NNT) and 1/10 (the NNT). Alternatively, an ‘NNT-based reimbursement plan’ could be agreed with the pharmaceutical companies for covering drug expenses of 6 patients at the 7th treated, or 10 patients at the 11th treated. Applying a similar procedure in the setting of Asian patients with characteristics of the CONCUR study population, it would result in a negotiation with cost reduction ranging between 1/3 (lower limit of the 95% CI of the NNT) and 1/5 (the NNT).

Regorafenib has a complex mechanism of action that might never allow identification of biomarkers for patients selection [9]. Therefore, payer coverage determination that address clinical value in addition to statistically significant clinical...