Correlation of basal EGFR expression with pancreatic cancer grading but not with clinical outcome after gemcitabine-based treatment

Philip et al. [1] recently published the results of a phase III study in 745 patients with locally advanced/metastatic pancreatic ductal adenocarcinoma (PDAC) treated either with gemcitabine and the anti-epidermal growth factor receptor (EGFR) cetuximab or with gemcitabine alone. This trial was based on evidence from earlier studies that suggested the combination had sufficient activity to warrant further testing but failed to meet its primary end point of improving overall survival (OS). However, the combination of gemcitabine with the epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) erlotinib translated into a significant improvement of OS [2]. Although increase in tumor control rates and association between rash and outcome seen in the gemcitabine + erlotinib study suggested that therapeutic benefit is confined to a subset of patients, in both trials analysis of EGFR expression failed to reveal a correlation with outcome. No correlation with OS was also observed in patients treated with single-agent gemcitabine [1].

However, previous studies showed a correlation of EGFR expression with grading and prognosis in PDAC patients who underwent only surgical treatment [3]. Therefore, we carried out an immunohistochemical analysis of EGFR in 100 Caucasian patients who underwent PDAC resection and were treated with gemcitabine in order to evaluate the correlation with (i) histological grading and (ii) outcome. Furthermore, we evaluated by uni-/multivariate analysis the role of stage (I–II/III–IV), lymph node/neural infiltration (yes/no) and resection margin (R0/R1).

EGFR staining was detectable at membrane and cytoplasmatic level (Figure 1A) in 84% and 82% of the patients, respectively. The values of EGFR expression, as evaluated by a total score from the analysis of both the number of positive cells and the staining intensity [4], ranged between 0 and 10 (median = 7) (Figure 1B and C). EGFR expression was significantly higher in grade 3 PDAC (P = 0.036, ‘Mann–Whitney test’). The histological differentiation resulted as a prognostic factor, with median OS of 24.8 [95% confidence interval (CI) 15.8–33.7] versus 11.1 months (95% CI 0.2–22.1) in patients with grade 1/2 and grade 3 tumors, respectively (P = 0.018, ‘log-rank test’ (Figure 1D). Similarly, patients with grade 1/2 and grade 3 PDAC had median Progression Free Survival (PFS) of 16.6 (95% CI 11.4–21.8) and 7.3 (95% CI 5.3–9.2) months, respectively (P = 0.007). Among other possible prognostic factors, only lymph node-positive status was correlated with significantly shorter OS and PFS (P = 0.016 and 0.006, respectively). In the Cox proportional hazards model, both grade 3 and lymph node-positive status resulted independent predictive parameters of death (Hazard Ratio (HR) = 2.0, 95% CI 1.1–3.8, P = 0.036 and HR = 3.1, 95% CI 1.1–8.6, P = 0.033, respectively) and progression risk (HR = 2.2, 95% CI 1.2–4.0, P = 0.012 and HR = 3.3, 95% CI 1.3–8.3, P = 0.012, respectively).

In contrast, no correlation was observed between EGFR expression and both PFS and OS (Figure 1E), as well as with stage, lymph node/neural infiltration and resection margin. The lack of correlation between EGFR expression and outcome in these patients might be caused by several factors, including modulation of EGFR expression/phosphorylation or related pathways in the relapse/metastatic tumors, which might then differ from resected specimens. Previous studies showed that resistance to cetuximab–gemcitabine in PDAC xenografts was caused by persistent mitogen-activated protein kinase activation and impaired EGFR internalization, associated with constitutive ErbB3 signaling [5].

In conclusion, EGFR expression is correlated with PDAC grading, but it lacks predictive value with respect to outcome in gemcitabine-treated patients both in the palliative and in the adjuvant setting ([1], present study). Future trials should provide the platforms for additional necessary translational research to identify other biomarkers/targets that can improve gemcitabine activity in PDAC.

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Figure 1. (A) Examples of EGFR staining from TMA sections obtained from paraffin-embedded tumor material (from four different tumor areas for each patient), incubated with the mAb from the EGFR pharmDX Kit, according to manufacturer’s instruction; left panels: TMA slide (×1 magnification) and a single spot of PDAC sample (×4); center panels: complete EGFR staining of cytoplasm and membrane (×20); right panels: negative and positive control of EGFR staining (×20). (B) EGFR staining results were evaluated using a four-tier system including the analysis of both the number of positive cells and the staining intensity. All slides were reviewed by three pathologists who also evaluated the amount of tissue loss, background staining and overall interpretability before the formal EGFR reactivity evaluation. (C) World Health Organization histological grading and EGFR expression levels (evaluated as described previously [3]) in 100 radically resected PDAC patients, enrolled from 2004 to 2008, at one center, Pisa University Hospital, to guarantee reliability of sampling, histological grading and immunohistochemistry analysis, as well as evaluation of clinical outcome. (D) Kaplan–Meier curves in gemcitabine-treated patients with grade 1/2 and grade 3 tumors and (E) curves in gemcitabine-treated patients with EGFR expression above (‘high’, OS = 22.2, 95% CI 13.1–31.4) and below (‘low’, OS = 28.8, 95% CI 13.7–43.9) the median total score. Clinical data were available for 78 patients, with median OS of 22.3 months (95% CI 16.0–28.5), event rate of 73% and median follow-up of surviving patients of 27.4 months (range 1.6–63.6), EGFR, epidermal growth factor receptor; TMA, tissue microarray; PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval; OS, overall survival.

References


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