6512 POSTER DISCUSSION

A randomized phase II trial of two different four-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel

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Background: PEFG regimen (P: cisplatin, E: epirubicin, F: 5-fluorouracil, G: gemcitabine) prolonged significantly progression-free (PFS) and overall survival (OS) of patients with advanced pancreatic adenocarcinoma (PA) with respect to standard gemcitabine (Reni, Lancet Oncol 2005). The current trial was aimed to assess whether the replacement of E with docetaxel (D) may improve 6 months PFS (PFS6).
Material and Methods: Chemo-naive patients with stage III or metastatic PA, age 18−75 y, Karnofsky performance status (PS) >50 received P (30 mg/m^2 day 1), G (800 mg/m^2 day 1) and capecitabine (1250 mg/m^2/day days 1 to 14) and were randomized to receive either D at 25−30 mg/m^2 day 1 (arm A: PDXG regimen) or E at 30 mg/m^2 day 1 (arm B: PEXG regimen). Cycles were repeated every 14 days for a maximum of 6 months. The Fleming design was used to calculate the sample size on the probability of being PFS6 (primary endpoint). Assuming P0 = 40% and P1 = 60%, a 0.05 and b 0.10, the study was to enroll 52 patients per arm. The regimen had to be considered of interest with >26 patients being PFS6.
Results: Between July 2005 and September 2008, 105 patients were enrolled at a single institution, stratified by stage and randomized (53 arm A). Patients' characteristics were (A/B): median age 61/59, PS > 70 92/88%, metastatic disease 66/65%; CA19.9 >upper limit of laboratory normal (ULN) 87/90%, median CA19.9 820/755 UI/mL. All patients are assessable for the primary endpoint: PFS6 was 59/56%. Median and 1 y OS was 10.7 and 41% in arm A and 10.7 and 43% in arm B. A partial response was observed in 60/37% of patients (p = 0.01). Among assessable patients with basal CA19.9 value >ULN (37 per arm), a major biochemical response (reduction >89%) was observed in 44/33% and a minor biochemical response (reduction between 50 and 89%) in 42/33% of patients (p = 0.03). No significant differences in quality of life were observed between arms. Altogether, 248 cycles of PDXG and 260 cycles of PEXG were administered. Main per cycle G3−4 toxicity was: neutropenia 4/13% (p = 0.0005), thrombocytopenia 2/4%, anemia 4/4%, fatigue 6/4%.
Conclusions: PEXG yielded similar results when compared to prior series treated by PEFG, suggesting that capecitabine may replace F. The inclusion of D instead of E yielded more objective and biochemical responses and less G3−4 neutropenia but did not improve PFS and OS. The present trial confirms the relevant impact on outcome of advanced PA of four-drug regimens.

6513 POSTER DISCUSSION

Successful prevention of symptomatic thromboembolic events by the low molecular weight heparin enoxaparin in patients with advanced pancreatic cancer – results of the CONKO 004 trial

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Objective: Patients (pts) with advanced pancreatic cancer (APC) are at increased risk for potentially letal venous thromboembolic events (VTE). There are conflicting data about the efficacy and safety of low molecular weight heparin (LMWH) used in different dosages for prevention of VTE in various cancers. LMWH are also under discussion to improve overall survival (OS) in malignancy. Our pilot study proved the feasibility of the LMWH enoxaparin (E) added to chemotherapy in pts with APC. So we consequently started this open, prospective, randomized, multicenter study (CONKO 004) to investigate the value of E in pts with APC.
Methods: Chemotherapy naive pts with histologically or cytologically confirmed APC were randomized to receive or not to receive LMWH (E 1 mg/kg once daily) simultaneously to palliative systemic chemotherapy. Primary endpoint of this trial was the reduction of symptomatic VTE (sVTE). Toxicity, time to progression (TTP) and OS were among the secondary endpoints of the study. This trial was approved by the ethics committees of the participating centers.
Results: The study was closed after recruitment of 312 pts in January 2009 according to a predefined event rate of sVTE. After a median follow-up of 30.4 weeks (w) the ITT-analysis resulted in a significant risk reduction of sVTE from 15% (22/152) in the observation group (O) to 5% (8/160) in the E group. The median time to sVTE in the E group was 19.6 [1.1;33] w versus 11.4 [0.4;45.4] w in the observation group. Major bleeding rates were 9.9% for O and 6.3% for E. In each group there was one tumor-related fatal hemorrhage. The preliminary data analysis (OS 208/312 pts; TTP 230/312 pts) illustrates no significant difference in OS (O:29w vs. E:31w) and TTP (O:19w vs. E:22w).
Conclusions: The prophylactic use of enoxaparin in pts with APC is effective and safe for the primary prevention of sVTE applied simultaneously to chemotherapy. Definitive results on OS and TTP are pending.

6514 POSTER DISCUSSION

Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial

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Background: There is no established treatment for pancreatic neuroendocrine tumors (NET) after chemotherapy failure. Octreotide controls symptoms and may affect tumor growth. In patients with progressive disease at study entry, estimated 6-month progression-free survival (PFS) was 28% (Panzuto. *Ann Oncol.* 2006;17:461–466; Hobday, ASCO 2006). Everolimus is an oral inhibitor of mTOR (mammalian target of rapamycin), a key enzyme regulating protein synthesis, cell growth, cell proliferation, and angiogenesis.
Methods: This phase II study assessed response rate (RR) and PFS in subjects with metastatic pancreatic NET who progressed (RECIST) during or after chemotherapy (RADIANT-1, NCT00363051). Subjects were stratified according to prior and ongoing use of depot octreotide therapy. Stratum 1: everolimus (10 mg PO daily) alone, stratum 2: everolimus and octreotide long-acting release (LAR). Tumor (RECIST) was assessed at baseline and every 3 months.
Results: 115 subjects were enrolled in stratum 1, 45 in stratum 2. RR by central radiology was 9.6% in stratum 1, 4.4% in stratum 2. Median PFS was 9.7 months in stratum 1, 16.7 months in stratum 2. Median overall survival was 24.9 months in stratum 1 and not yet reached in stratum 2. Twenty four-month survival was 54.7% in stratum 2. A chromogranin-A response (decrease by 50% or normalization) was noted in 50.7% of subjects in stratum 1, 60% in stratum 2. At the time of data cut, 20.9% of subjects in stratum 1 and 24.4% in stratum 2 were still on treatment. Treatment was well tolerated, and most adverse events (AEs) were mild to moderate. The most frequent AEs (all grades) suspected to study treatment were (% stratum 1/% stratum 2) stomatitis (45/49), rash (40/44), diarrhea (39/31), fatigue (31/36), nausea (30/33), and headache (22/7). Most common suspected grade 3 AEs were asthenia in stratum 1 and thrombocytopenia in stratum 2. Only 4% had suspected grade 4 AEs. Grade 1/2 pneumonitis or interstitial lung disease occurred in 8.8%, with no grade 3/4 events. There were no major differences in safety between the 2 strata.
Conclusion: Daily everolimus, with or without concomitant octreotide LAR, demonstrates antitumor activity and is well tolerated in patients with low-intermediate grade pancreatic NET after failure of prior systemic chemotherapy.
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