

ARCI: Nelfinavir, a hypoxia-modifying agent, in combination with chemoradiotherapy (CRT) in locally-advanced pancreatic cancer (LAPC)—Mechanism and clinical outcomes.

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Journal of Clinical Oncology 2015 33:15_suppl, e15279-e15279

Abstract

Background: In LAPC, additional benefit of CRT over chemotherapy is uncertain. Optimising local therapy for a subset that never develops distant disease may prolong survival. Nelfinavir is thought to enhance radiosensitivity through hypoxia reduction by increasing tumour blood flow.

Methods: A non-randomised, single centre phase II study, in FDG-PET-selected patients with histologically proven LAPC. CRT consisted of: nelfinavir 1250 mg bd (days -3 to 45); gemcitabine 300 mg/m² & cisplatin 30 mg/m² (days 2, 9, 23 & 30); concurrent radiotherapy: 59.4 Gy/33# to primary tumour, 50.4 Gy/28# to regional nodes. Adjuvant gemcitabine was given for 6 months. Primary endpoint: 1 year overall survival (OS); secondary endpoints included: toxicity, response rate, resectability, median progression free survival (PFS), OS and local PFS. 6 patients had sequential dynamic ¹⁸F-fluoromisonidazole PET (FMISO-PET) and perfusion CT (pCT) before and after 6-7 days of nelfinavir (given from day -8).

Results: 23 patients entered between Feb 2010-July 2014. The trial was stopped because of unavailability of nelfinavir in Europe. 3 patients did not complete treatment (1 each of PE, biliary sepsis, stroke). Common G3/4 toxicities: thrombocytopenia/leukopenia (both 35%), diarrhoea (17%), nausea/vomiting (17%), fatigue (13%). 1 yr and median OS: 76.7% (95% CI 52.8-89.6) and 17.4 months (95% CI 12.7-22.8) respectively. 1 yr PFS and Local PFS: 36.8% (16.5-57.5) and 52.9% (95% CI 25.2-74.4) respectively. Mean FDG SUV_{max} reduction was 39% (p < 0.001) and was ≥60% in 29% of patients. 2 patients became resectable. 4/6 patients had reduced FMISO retention and increased pCT derived blood flow (BF) post-nelfinavir. Mean change in FMISO-k₃ (2 tissue compartmental model) -50.3% vs 6% and BF 20.1 vs -7.1% in responders vs non-responders. 8/13 demonstrated a reduction in pAKT in peripheral blood mononuclear cells.

Conclusions: Nelfinavir with CRT is well tolerated with promising outcomes, as these patients were not pre-selected through induction chemotherapy. Modulation of hypoxia & BF by nelfinavir was demonstrated. A randomised phase II study, SCALOP2, opens in 2015. [Clinical trial information: 2008-006302-42.](#)

