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Update on the toxicity and response of a phase I trial of concurrent, daily gefitinib and radiation or chemo-radiation for patients with locally advanced squamous cell cancer of the head and neck (LASCCHN)

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Background: The purpose of this study is to establish the safety profile of daily gefitinib given with concurrent RT alone or combined with chemotherapy (CT)/RT in previously untreated patients (pts) with LASCCHN. Additional endpoints include defining the feasibility/toxicity profile of maintenance daily gefitnib beginning 4–8 weeks after the completion of the RT or RT/CT for a period not to exceed 2 years.
Materials and Methods: Pts with SCCHN were eligible to be treated with daily gefitinib (250, 500 mg) when combined with either altered fraction RT (72 Gy) alone or CT/RT (70 Gy) in pts with intermediate or locally advanced stage disease respectively. Once the safety profile of gefitinib and RT was established, additional pts would be accrued combining daily gefitinib (250, 500 mg) with weekly cisplatin (30 mg/m^2) and concurrent RT. All pts receive maintenance gefitinib for a period of 2 years. All pts receive ~7–10 days of gefitinib prior to beginning treatment; repeat biopsies are attempted to try to assess for molecular/immunohistochemical changes. Gefitinib is restarted once all mucosal or skin toxicity is $\leqslant$grade 2.
Results: To date, 14 pts have been enrolled. Ten pts presented with tumors in the oropharynx; 4/14 in the supraglottic or glottic larynx. The first 8 pts with stage **III** LAHNC have completed RT/gefitinib (5 pts at 250 mg and 3 pts at 500 mg). Six pts with stage IV LAHNC have enrolled to receive RT/CT/gefitinib (250 mg). To date, 4/6 pts have completed treatment. No pts on Cohort 1 or 2 experienced a grade 4 toxicity. Grade 3 toxicities included mucositis, and skin reactions related to RT as well as grade 3 nausea related to CT or amifostine. In cohort 3, 1 pt had G4 diarrhea resulting in hospitalization. This pt completed RT but was unable to continue with CT or the gefitinib. Two pts on cohort 3 had G3 dehydration. One patient had G4 hypokalemia secondary to dehydration. Finally, 1 pt experienced a PE 4 weeks after RT/CT/gefitinib was completed. Clinically, 7/8 pts who completed gefitinib/RT experienced a CR above the clavicles with early follow-up. One pt failed locally in the primary site; an additional pt failed only distantly in a single site in liver. The median follow-up in the pts treated with gefitinib/RT is ~15.5 months. Three of four pts eligible to restart gefitinib were unable to tolerate maintenance dosing at 500 mg; the protocol was amended to allow for 250 mg daily gefitinib. One pt had protracted mucositis and restarted gefitinib at 5 months post treatment but was unable to tolerate it. Three pts have just completed CT/RT + gefitinib treatment.
Conclusion: Gefitinib + RT was well tolerated at both the 250 and 500 mg levels with no significant increase in RT toxicity. An 87.5% clinical CR rate was observed in this initial group of intermediate stage pts. As expected, increased toxicity has been observed in the patients receiving CT/RT + gefitinib with 2 DLTs seen in the first 6 pts related to the treatment.

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Pathological complete response rate in esophageal cancer after endoscopically delivered intratumoral (IT) injections of TNFerade combined with neoadjuvant chemoradiotherapy (CRT): a phase I/II trial

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Background: Despite neoadjuvant therapy and aggressive surgical resections, the prognosis for esophageal cancer remains poor. TNFerade is a second-generation replication-deficient adenovector, carrying the transgene encoding for human TNF-α, regulated by the radiation-inducible promoter Egr-1. Two completed phase **I** studies of TNFerade combined with fractionated radiotherapy, and an ongoing phase **II** study of TNFerade with CRT in pancreatic cancer support the safety and activity of this agent.
Material and Methods: Multicenter dose-escalating design to demonstrate feasibility, safety and maximum-tolerated dose (MTD) of TNFerade combined with neoadjuvant CRT in patients with resectable stage **II** and **III** esophageal cancer (by endoscopic ultrasound, EUS). Inclusion criteria included: resectable squamous (SQ) or adenocarcinoma (A); age <75; KPS $*$ 70%; acceptable biochemical, hematologic profiles. TNFerade was administered by intratumoral injection once weekly $\times$ 5 weeks concurrently with radiotherapy (45 Gy/25 fx/5 weeks) and 5-FU (1000 mg/m2/day for 96 hrs) plus cisplatin (75 mg/m2) on Days 1 and 29. IT TNFerade injections were given via EUS- or endoscopic-guided technique (per study site preference) at doses of 4×10^8 to 4×10^{11} pu (inter-patient escalation in 1 log increments). Study endpoints included safety and histopathologic complete response rate (from resection specimens).
Results: 18 patients (4 dose cohorts) have been enrolled and enrollment continues at the top dose level (4×10^{11} pu). The majority of tumors (17/18) are cT3 (13 T3N1, 3 T3N0, 1 T3NX) and adenocarcinomas (15/18 A, 3/18 SQ). Repeated endoscopic administration of TNFerade during chemoradiotherapy was feasible and well-tolerated; the MTD has not yet been reached. With the exception of one Grade 3 esophagitis, AEs possibly related to TNFerade have all been NCI grade 1–2 and include fatigue (31%), pain (19%), esophagitis (19%), and rigors, nausea, vomiting, and decreased appetite (13% each). To date, all serial serum TNF-α levels are <100. Neutralizing antibodies to adenovirus were present (>1:50) in 33% at baseline and elevated in 9/11 at end of treatment. To date, pathological assessment was complete on 11, with pathologic complete response in 1/7 (14%) treated at 4×10^8 pu and 3/4 (75%) treated at 4×10^9 pu. There was no evidence of increased operative mortality or perioperative morbidity. One patient death occurred secondary to fistula-related complications prior to surgery was reviewed and concluded as not related to TNFerade or IT injection.
Conclusions: Concurrent weekly endoscopic IT injections of TNFerade with chemoradiation is feasible. This regimen is well tolerated with preliminary data suggestive of TNFerade dose-related pathological down staging. Accrual and data assessment continue; and the phase **II** portion of this study at the MTD for TNFerade is planned.

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Effects of celecoxib and irradiation treatment on prostate cancer cell lines

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The selective cyclooxygenase-2 inhibitor celecoxib has been shown to inhibit tumor cell growth independently from its inhibitory action on cyclooxygenase-2 (COX-2) and to increase the efficacy of ionizing radiation *in vitro* as well as in animal models. The growth inhibitory effects of celecoxib had been attributed to its pro-apoptotic action. In this context, apoptosis induction in Jurkat T-lymphoma cells occurred via a mitochondrial death pathway that could not be inhibited by over-expression of Bcl-2. Similarly, Bcl-2 overexpression did not protect against celecoxib induced apoptosis in LNCaP and PC-3 prostate cancer cell lines. However, the mechanisms of celecoxib mediated radiosensitization are still unclear. The aim of the present study was to analyse the proapoptotic and radiosensitizing potential of celecoxib in four human prostate cancer cell lines and to analyse the significance of the pro-apoptotic Bcl-2 protein Bax in this process. To this end, the impact of the celecoxib on the induction of apoptosis, cell cycle distribution as well as clonogenic cell survival was evaluated in four different prostate cancer cell lines (LNCaP/p53$^{+/+}$/androgen–responsive, and PC3/p53$^{-/-}$, DU-145mock, Du145bax/androgen-nonresponsive).
At concentrations below 25 μM celecoxib caused rapid morphological changes, cell cycle arrest and growth inhibition without substantial apoptosis induction. In addition, no radiosensitization in terms of decreased clonogenic cell survival could be observed. In contrast, at drug concentrations $\geqslant$ 25 μM celecoxib dramatically increased cell death and clonogenic cell kill irrespective of the cellular expression levels of Bax. These findings provide evidence for a Bax-independent pro-apoptotic and radiosensitizing action of celecoxib. Since radiation-induced apoptotic cell death was altered in cells without Bax, our data support the hypothesis that the cell death promoting effects of irradiation and celecoxib are mediated by distinct mechanisms of action.
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