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GASTROINTESTINAL NEWS

Newsletter di aggiornamento sui tumori gastrointestinali

GASTROINTESTINAL NEWS nel 2007 si presenta rinnovato sia nella veste che nel contenuto. Nato per iniziativa del comitato scientifico e coordinato da Intermedia, mantiene la pubblicazione quindicinale e continua ad occuparsi di cancro gastrointestinale. Le news non verranno più tradotte in italiano, ma pubblicate in lingua inglese e, una volta al mese, verrà proposto un commento su un particolare articolo, preparato da un componente del comitato scientifico.

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Clinical Benefit With Docetaxel Plus Fluorouracil and Cisplatin Compared With Cisplatin and Fluorouracil in a Phase III Trial of Advanced Gastric or Gastroesophageal Cancer Adenocarcinoma: The V-325 Study Group - Journal of Clinical Oncology 2007; Volume 25, Number 22, August 1: Pages 3205 - 3209 (abstract)

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NEWS DALLA RICERCA

Clinical Benefit With Docetaxel Plus Fluorouracil and Cisplatin Compared With Cisplatin and Fluorouracil in a Phase III Trial of Advanced Gastric or Gastro-esophageal Cancer Adenocarcinoma: The V-325 Study Group

Jaffer A. Ajani, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Constenla, Corrado Boni, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Cindy Marabotti, Eric Van Cutsem

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Journal of Clinical Oncology 2007; Volume 25, Number 22, August 1: Pages 3205 - 3209

Purpose: For patients with advanced gastric or gastroesophageal cancer (AGGEC) providing clinical benefit with improved palliation is highly desirable. However, a prospective evaluation of clinical benefit in AGGEC patients has never before been reported in a phase III setting.

Patients and Methods: In a multinational trial (V325), 445 patients were randomly assigned and treated with either docetaxel plus cisplatin and fluorouracil (DCF) or cisplatin and fluorouracil (CF). Clinical benefit was prospectively evaluated in this trial as a secondary end point. The primary measure for clinical benefit analysis was time to definitive worsening by one or more categories of Karnofsky performance status (KPS). Secondary clinical benefit end points included time to 5% definitive weight loss, time to definitive worsening of appetite by one grade, pain-free survival (defined as time to first appearance of pain), and time to first cancer pain-related opioid intake. Clinical benefit assessments were recorded at each clinic visit.

Results: Clinical benefit assessments were performed in more than 75% of patients throughout V325. DCF significantly prolonged time to definitive worsening of KPS compared with CF (median, 6.1 *v* 4.8 months; hazard ratio, 1.38; 95% CI, 1.08 to 1.76; log-rank P = .009). Although time to definitive weight loss and time to definitive worsening of appetite favored DCF, the results were not statistically significant. Pain-free survival and time to first cancer pain-related opioid intake were comparable.

Conclusion: To our knowledge, V325 is the first phase III trial to report clinical benefit in AGGEC patients. Clinical benefit was assessed beyond protocol-specific chemotherapy. The addition of D to CF not only significantly improved clinical benefit but also improved quality of life, time to progression, and overall survival compared with CF.

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Quality of Life With Docetaxel Plus Cisplatin and Fluorouracil Compared With Cisplatin and Fluorouracil From a Phase III Trial for Advanced Gastric or Gastro-esophageal Adenocarcinoma: The V-325 Study Group

Jaffer A. Ajani, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Constenla, Corrado Boni, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Lucile Awad, Eric Van Cutsem

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Journal of Clinical Oncology 2007; Volume 25, Number 22, August 1: Pages 3210 - 3216

Purpose: Therapy of patients with advanced gastric or gastroesophageal junction cancer should provide symptom relief and improve quality of life (QOL) because most patients are symptomatic at baseline. Using validated instruments, we prospectively assessed QOL (even after completion of protocol treatment) as one of the secondary end points of the V325 phase III trial.

Patients and Methods: Four hundred forty-five patients randomly received either docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 each on day 1 plus fluorouracil 750 mg/m^2/d continuous infusion on days 1 to 5 every 3 weeks (DCF) or cisplatin 100 mg/m^2 on day 1 plus fluorouracil 1,000 mg/m^2/d continuous infusion on days 1 to 5 every 4 weeks (CF). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and, where available, the EuroQOL EQ-5D questionnaire were administered every 8 weeks from baseline until progression and then every 3 months. Time to definitive deterioration of QOL parameters was analyzed.

Results: The proportions of patients having assessable EORTC QLQ-C30 and EQ-5D questionnaires at baseline were 86.0% and 78.7% with DCF, respectively, and 89.7% and 92.8% with CF, respectively. Time to 5% deterioration of global health status (primary end point) significantly favored DCF over CF (log-rank test, $P = .01$). QOL was preserved longer for patients on DCF than those on CF for all time to deterioration analyses, demonstrating the statistical superiority of DCF compared with CF.

Conclusion: V325 represents the largest trial with the longest prospectively controlled evaluations of QOL during protocol chemotherapy and follow-up in patients with advanced gastric or gastroesophageal junction cancer. In V325, advanced gastric or gastroesophageal junction cancer patients receiving DCF not only had statistically improved overall survival and time to tumor-progression, but they also had better preservation of QOL compared with patients receiving CF.

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Docetaxel, Cisplatin, and Fluorouracil; Docetaxel and Cisplatin; and Epirubicin, Cisplatin, and Fluorouracil As Systemic Treatment for Advanced Gastric Carcinoma: A Randomized Phase II Trial of the Swiss Group for Clinical Cancer Research

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Journal of Clinical Oncology 2007; Volume 25, Number 22, August 1: Pages 3217 - 3223

Purpose: This randomized phase II trial evaluated two docetaxel-based regimens to see which would be most promising according to overall response rate (ORR) for comparison in a phase III trial with epirubicin-cisplatin-fluorouracil (ECF) as first-line advanced gastric cancer therapy.

Patients and Methods: Chemotherapy-naïve patients with measurable unresectable and/or metastatic gastric carcinoma, a performance status ≤1, and adequate hematologic, hepatic, and renal function randomly received eight 3-weekly cycles of ECF (epirubicin 50 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and fluorouracil [FU] 200 mg/m^2/d on days 1 to 21), TC (docetaxel initially 85 mg/m^2 on day 1 [later reduced to 75 mg/m^2 as a result of toxicity] and cisplatin 75 mg/m^2 on day 1), or TCF (TC plus FU 300 mg/m^2/d on days 1 to 14). Study objectives included response (primary), survival, toxicity, and quality of life (QOL).

Results: ORR was 25.0% (95% CI, 13% to 41%) for ECF, 18.5% (95% CI, 9% to 34%) for TC, and 36.6% (95% CI, 23% to 53%) for TCF (n = 119). Median overall survival times were 8.3, 11.0, and 10.4 months for ECF, TC, and TCF, respectively. Toxicity was acceptable, with one toxic death (TC arm). Grade 3 or 4 neutropenia occurred in more treatment cycles with docetaxel (TC, 49%; TCF, 57%; ECF, 34%). Global health status/QOL substantially improved with ECF and remained similar to baseline with both docetaxel regimens.

Conclusion: Time to response and ORR favor TCF over TC for further evaluation, particularly in the neoadjuvant setting. A trend towards increased myelosuppression and infectious complications with TCF versus TC or ECF was observed.

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Detection of distant metastases in patients with oesophageal or gastric cardia cancer: a diagnostic decision analysis

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British Journal of Cancer 2007; Volume 97, Number 7, Oct 8: Pages 868 - 876

Computed tomography (CT) is presently a standard procedure for the detection of distant metastases in patients with oesophageal or gastric cardia cancer. We aimed to determine the additional diagnostic value of alternative staging investigations. We included 569 oesophageal or gastric cardia cancer patients who had undergone CT neck/thorax/abdomen, ultrasound (US) abdomen, US neck, endoscopic ultrasonography (EUS), and/or chest X-ray for staging. Sensitivity and specificity were first determined at an organ level (results of investigations, i.e., CT, US abdomen, US neck, EUS, and chest X-ray, per organ), and then at a patient level (results for combinations of investigations), considering that the detection of distant metastases is a contraindication to surgery. For this, we compared three strategies for each organ: CT alone, CT plus another investigation if CT was negative for metastases (one-positive scenario), and CT plus another investigation if CT was positive, but requiring that both were positive for a final positive result (two-positive scenario). In addition, costs, life expectancy and quality adjusted life years (QALYs) were compared between different diagnostic strategies. CT showed sensitivities for detecting metastases in celiac lymph nodes, liver and lung of 69, 73, and 90%, respectively, which was higher than the sensitivities of US abdomen (44% for celiac lymph nodes and 65% for liver metastases), EUS (38% for celiac lymph nodes), and chest X-ray (68% for lung metastases). In contrast, US neck showed a higher sensitivity for the detection of malignant supraclavicular lymph nodes than CT (85 *vs* 28%). At a patient level, sensitivity for detecting distant metastases was 66% and specificity was 95% if only CT was performed. A higher sensitivity (86%) was achieved when US neck was added to CT (one-positive scenario), at the same specificity (95%). This strategy resulted in lower costs compared to CT only, at an almost similar (quality adjusted) life expectancy. Slightly higher specificities (97-99%) were achieved if liver and/or lung metastases found on CT, were confirmed by US abdomen or chest X-ray, respectively (two-positive scenario). These strategies had only slightly higher QALYs, but substantially higher costs. The combination of CT neck/thorax/abdomen and US neck was most cost-effective for the detection of metastases in patients with oesophageal or gastric cardia cancer, whereas the performance of CT only had a lower sensitivity for metastases detection and higher costs. The role of EUS seems limited, which may be due to the low number of M1b celiac lymph nodes detected in this series. It remains to be determined whether the application of positron emission tomography will further increase sensitivities and specificities of metastases detection without jeopardising costs and QALYs.

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Targeting Cyclooxygenase-2 and the Epidermal Growth Factor Receptor for the Prevention and Treatment of Intestinal Cancer

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Cancer Research 2007; Volume 67, Number 19, October 1: Pages 9380 - 9388

Clinical and animal studies indicate a role for cyclooxygenase-2 (COX-2) and the epidermal growth factor receptor (EGFR) in the development and progression of intestinal polyps and cancers. Although this combination of enzyme inhibition has shown synergy in intestinal polyp and tumor models, the exact mechanism for these effects remains undefined. Therefore, we sought to define the molecular mechanisms through which this process occurs. We observed a significant reduction in the number and size of small intestinal polyps in $APC^{min+/-}$ mice treated with either celecoxib (a selective COX-2 inhibitor) or erlotinib (Tarceva, an EGFR inhibitor). However, in combination, there was an overall prevention in the formation of polyps by over 96%. Furthermore, we observed a 70% reduction of colorectal xenograft tumors in mice treated with the combination and microarray analysis revealed genes involved in cell cycle progression were negatively regulated. Although we did not observe significant changes in mRNAs of genes with known apoptotic function, there was a significant increase of apoptosis in tumors from animals treated with the combination. The inhibition of EGFR also induced the down-regulation of COX-2 and further inhibited prostaglandin E_2 formation. We observed similar effects on the prevention of intestinal adenomas and reduction of xenograft tumor volume when nonselective COX inhibitors were used in combination with erlotinib. Together, these findings suggest that the inhibition of both COX-2 and EGFR may provide a better therapeutic strategy than either single agent through a combination of decreased cellular proliferation and prostaglandin signaling as well as increased apoptosis.

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APPUNTAMENTI

AVANZAMENTI NELLA TERAPIA DEL CARCINOMA COLORETTALE

Milano, 9-16 novembre 2007 - Oncologia Falck, Ospedale Niguarda Ca' Granda
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FOCUS IN ONCOLOGIA

Dagli Off label alla gestione del File F in oncologia
Melegnano, 22 novembre 2007 - Azienda Ospedaliera Melegnano
Per scaricare il programma consulta il sito web: www.medinews.it (Società Scientifiche-AIOM-Appuntamenti)

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X INTERNATIONAL SYMPOSIUM ON PLATINUM COORDINATION COMPOUNDS IN CANCER CHEMOTHERAPY

Verona, 30 novembre-3 dicembre 2007 - Palazzo della Gran Guardia, Piazza Brà
Organizzazione: Department of Oncology Mater Salutis Hospital Legnago, Department of Medicine and Public Health, Section of Pharmacology University of Verona, *in collaborazione con* Sendo, South Europe New Drug Organization
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Per scaricare il programma consulta il sito web: www.ispcc2007.org

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1° CONVEGNO NAZIONALE MULTIDISCIPLINARE DI MEDICINA

Convegno di Oncologia: "Prevenzione, Diagnosi, Stadiazione, Terapia e Supporto Psicologico al malato e ai parenti per tumori del Colon Rettale, Polmoni e Mammella"
Evento patrocinato AIOM - Presidente: Prof. Edmondo Terzoli
Roma, 17-20 gennaio 2008 - Nuova Fiera di Roma, Angelo Vescovali, Entrata Nord
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