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Thirty-Seventh Annual Meeting

May 12-15, 2001  
San Francisco, CA

ASCO™ 

**Thirty-Seventh  
Annual Meeting of the  
American Society of Clinical Oncology  
May 12–15, 2001  
San Francisco, California**

*Program/Proceedings*



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**Symptom Management**

**1527 ORAL PRESENTATION, MON, 9:30 AM - 12:30 PM**

**Establishing the Dose of the Oral NK-1 Antagonist MK-869 for Chemotherapy Induced Nausea and Vomiting.** S. P. Chawla, R. J. Gralla, P. J. Hesketh, S. M. Grunberg, M. E. Elmer, K. J. Horgan; Century City Hospital, Los Angeles, CA; Columbia University, New York, NY; St. Elizabeth's Medical Center, Boston, MA; University of Vermont, Burlington, VT; Merck Research Laboratories, West Point, PA

MK-869 (M), a potent and selective NK-1 receptor antagonist, reduced chemotherapy induced nausea and vomiting (CINV) after cisplatin (C) when given in combination with granisetron and dexamethasone (D) (N. Engl J. Med 340:190-195, 1999). To define the appropriate dose of M, 563 patients (mean age 56, 42% female) receiving their initial C  $\geq$  70mg/m<sup>2</sup> were assigned in a blinded fashion to four groups: (I) M (375 mg PO) one hour prior to C on day 1 and M (250 mg PO) on days 2-5; (II) M (125 mg PO) prior to C and M (80 mg P.O.) on days 2-5; (III) M (40 mg PO) prior to C and M (25 mg P.O.) on days 2-5; (IV) M (placebo) prior to C and on days 2-5; All groups received ondansetron (32 mg IV) and D (20 mg P.O.) prior to C, and also received D (8 mg P.O.) on days 2-5. A preliminary analysis provided the data below. Conclusions: MK-869 125 mg on day 1, followed by 80 mg on subsequent days, provided excellent control of cisplatin-induced CINV and is an appropriate regimen for further evaluation. At all doses MK-869 was well tolerated.

**% OF PATIENTS WITH COMPLETE RESPONSE †**

Treatment Group (N)	Overall (Days 1-5)	Acute (Day 1)	Delayed (Days 2-5)
I (33)	67	91*	70*
II (204)	66**	83**	70**
III (115)	58**	76	64**
IV (205)	45	71	46

†Complete Response= no vomiting and no rescue therapy \* p<0.05, \*\*p<0.01; vs Group IV for subset(s) of concurrently enrolled patients.

**1529 ORAL PRESENTATION, MON, 9:30 AM - 12:30 PM**

**Recombinant Human Keratinocyte Growth Factor (rHuKGF) Prevents Chemotherapy-Induced Mucositis in Patients with Advanced Colorectal Cancer: A Randomized Phase II Trial.** S. J. Clarke, PhD MBBS, E. Abdi, PhD, I. D. Davis, PhD, F. M. Schnell, PhD, J. R. Zalcberg, PhD, J. Gutheil, PhD, C. Serdar, PhD, B. Yao, PhD, R. Heard, PhD, N. Meropol, PhD, L. S. Rosen, PhD; Royal Prince Alfred Hospital, Camperdown, Australia; Bendigo Health Care Group, Bendigo, Australia; Austin Repat Medical Center, Heidelberg, Australia; Central Georgia Assoc., Macon, GA; Peter MacCallum Cancer Institute, Victoria, Australia; Sidney Kimmel Cancer Center, San Diego, CA; Amgen, Inc., Thousand Oaks, CA; Fox Chase Cancer Center, Philadelphia, PA; UCLA Jonsson Cancer Center, Los Angeles, CA

Recombinant HuKGF is an epithelial specific growth factor, which has been shown in preclinical models to protect animals from gastrointestinal mucosal damage induced by chemotherapy or radiotherapy. A previously reported randomized phase I clinical trial in patients with advanced colorectal cancer (Meropol *et al.*, Proc ASCO, 19:2374, 2000) demonstrated that rHuKGF at doses  $\geq$  10  $\mu$ g/kg reduced the incidence of grade 2-4 oral mucositis caused by 5-fluorouracil (5-FU) chemotherapy as compared to placebo (43% and 67% respectively; p=0.06). To establish efficacy, we enrolled 64 additional patients with advanced colorectal cancer [42 M/22 F, median age 65 (range 37-88), median ECOG performance status of 1 (range 0-2)]. The patients were randomly assigned to receive 2 cycles of either rHuKGF 40  $\mu$ g/kg/day or placebo by IV bolus on days 1-3, followed by bolus 5-FU 425 mg/m<sup>2</sup>/day plus leucovorin 20 mg/m<sup>2</sup>/day on days 4-8 of a 28 day cycle. Analysis of results showed that incidence of Grade 2, 3, and 4 mucositis in two cycles combined was 78% in placebo (n=36) and 32% in rHuKGF group (n=28) [p=0.001]. A significant reduction in the duration (all patients) of mucositis was also observed (10.2 days for placebo and 3.4 days for rHuKGF; p=0.001). Recombinant HuKGF had no effect on median survival [71 weeks for rHuKGF group (95% CI 54-81) vs. 66 weeks for placebo group (95% CI 41-135)]. The most common treatment-related adverse events were mild to moderate skin-related events including rash, flushing, and edema (36% in rHuKGF-treated subjects and 22% in the placebo group). Asymptomatic and reversible increases in amylase and lipase were observed after rHuKGF administration. These results confirm and extend our previous clinical observations of the efficacy and safety profile of rHuKGF - reducing the incidence, severity and duration of chemotherapy-induced mucositis.

**1528 ORAL PRESENTATION, MON, 9:30 AM - 12:30 PM**

**Differential Time Course of Cisplatin Induced Acute Emesis with a 5-HT3 Antagonist or an NK1 Antagonist: Rationale for Combination Therapy.** K. J. Horgan, K. N. Eldridge, A. Carides, S. Van Belle, P. J. Hesketh; Merck and Company, Inc., West Point, PA; University Hospital Gent, Gent, Belgium; St. Elizabeth's Medical Center, Boston, MA

Neurokinin 1 receptor antagonists (NK1 RAs) show efficacy in reducing acute and delayed cisplatin-induced emesis. Their effects in delayed emesis are noteworthy and may distinguish this new class of antiemetic from 5-HT3 receptor antagonists (5-HT3 RAs) that have limited utility in delayed emesis. Optimal use of NK1 RAs is likely to involve combinations with existing agents. In an effort to identify a rationale for such combinations, we evaluated the time course of acute emesis in a trial comparing L-758,298(L), prodrug for the selective NK1 RA, MK-0869, with a 5-HT3 RA ondansetron(OND) in patients (pts) receiving 50 mg/m<sup>2</sup> cisplatin. 30 pts received 60 or 100 mg of L iv & 23 pts received a 32 mg dose of OND iv. The efficacy results of this trial have been previously reported (Proc ASCO 17:51a 1998). No acute vomiting rate: 37%, 52% with L and OND respectively (P=0.57). Historically, the frequency of acute emesis following this dose of cisplatin without prophylaxis should be virtually 100% with a median time to first emesis of <2 hours. The time course of acute vomiting following OND & L was quite distinct. The median time to first vomiting was 4.46hrs & 12.25hrs in the L and OND groups respectively. All acute failures in the L group occurred in the first 8h. These results support the hypotheses that later, but not 'early' acute vomiting episodes are primarily substance P mediated and that conversely, serotonin mediated mechanisms may play a more important role during the 'early' acute period. If these hypotheses are correct, a strong rationale exists to combine 5-HT3 RAs and NK1 RAs to optimize acute control. To date, the best control of acute cisplatin-induced emesis has been noted with the 3 drug combination of a 5-HT3 RA, a NK1 RA, and dexamethasone.

**Percentage of Patients with Acute Vomiting**

	0-8h	8-16h	16-24h	Overall (0-24h)
L-758,298 (30)	63	0	0	63
Ondansetron(23)	17	13	17	48

**1530 ORAL PRESENTATION, MON, 9:30 AM - 12:30 PM**

**Fluoxetine Versus Placebo in Advanced Cancer Outpatients: A Placebo-Controlled, Double-Masked Trial of the Hoosier Oncology Group.** M. J. Fisch, P. J. Loehrer, S. D. Passik, J. L. Kristeller, S. Jung, L. H. Einhorn; UT/MD Anderson Cancer Center, Houston, TX; Indiana University Cancer Center, Indianapolis, IN; Community Cancer Care Inc., Indianapolis, IN; Indiana State University, Terre Haute, IN

Depressive symptoms are prevalent in advanced cancer patients, and no standard of care exists regarding assessment and management of this clinical problem. Serotonin reuptake inhibitors such as fluoxetine are effective for major depression and well-tolerated in the medically ill. Controlled data are lacking regarding the efficacy of simple screening for depressive symptoms and treatment of those symptoms with an antidepressant. Advanced cancer outpatients were routinely screened with a two-question screening survey that assessed depressed mood and anhedonia. Patients with at least minimal depressive symptoms and no current or recent exposure to antidepressants were eligible for study inclusion regardless of their primary disease site or concurrent anti-cancer treatment. 163 outpatients with an advanced solid tumor and an expected survival between 3-24 months were randomized in a double-masked fashion to receive either fluoxetine 20 mg daily or placebo for a total of 12 weeks. Patients were stratified by performance status. Longitudinal assessments were performed every 3-6 weeks including quality of life (QOL), depression, and spiritual well-being. The primary objective was to compare the change in QOL (using the FACT-G) of patients treated with fluoxetine versus placebo. Secondary endpoints included assessment of depression and spiritual well-being. This is the largest controlled trial comparing an antidepressant to placebo in advanced cancer patients, and one of the first therapeutic trials in cancer patients involving the longitudinal assessment of spiritual well-being. The study has met its accrual goal and complete analysis of all endpoints will be presented at the meeting.