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A study of renal function of four infusions of Pamidronate 90 mg given over 60 minutes one week apart.

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As Bisphosphonates are found to be active in management of bone metastases by inhibition of osteolysis it is desirable to find the safe optimum dose and infusion rate. Nephrotoxicity might be dose limiting.
12 patients with bone metastases from Ca Breast (7) Ca Prostate (4) and Ca Bladder (1) were entered into an open non comparative trial and received Pamidronate 90 mg in 250 ml of Normal Saline over 1 hour weekly for 4 infusions.
Renal function was assessed by blood biochemistry, 51Cr EDTA Clearance on 5 occasions and 24 hour urine collections for Total Urinary Protein plus N.A.G. and B2 Microglobulin.
No significant changes in renal function were detected. The only toxicity was flu like symptoms, fever, chills (4 patients), phlebitis (1 patient), eye inflammation (1 patient)
Allowing for the small size of the sample it would appear that this dose and infusion rate has no detectable effect on renal function, and is a well tolerated induction schedule.

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FILGRASTIM WITH DOSE INTENSIFIED CDE CHEMOTHERAPY IN SMALL CELL LUNG CANCER

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To determine whether administration of filgrastim (G-CSF) will allow combination chemotherapy to be given every 14 days instead of 21, cyclophosphamide 1 G/m^2 day 1, doxorubicin 50 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1-3 (CDE) was given to patients together with filgrastim from days 4-14 inclusive for 6 cycles. The aim was to avoid dose reductions, but not to administer subsequent cycles until the ANC had exceeded 1.5 x 10^9/l and the platelet count was more than 100 x 10^9/l, with a maximum allowable delay of 21 days before withdrawal from the study. 42 patients with all stages of SCLC have entered on study to date, of whom 21 are evaluable with mean age 55.0 (range 41-66) and mean PS 0.9. 98 cycles have been given to date, and 22 episodes of neutropenic fever recorded, one of which was fatal but 16 pts (76%) have been able to receive either 5 or 6 cycles as planned (4 cycles n=2; 3 cycles n=2; 1 cycle n=1). Response was assessed after cycles 3 and 6 (maximum response CR 10: PR 9: PD 1: NE 1). Delays were seen in 26 cycles in 14 patients, principally as a result of thrombocytopenia. This study shows that with the use of filgrastim, full doses of intensified chemotherapy can be given safely to a high proportion of patients with small cell lung cancer.

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HIGH DOSE CHEMOTHERAPY WITH EPIRUBICIN (E) AND CYCLOPHOSPHAMIDE (C) PLUS HEMOPOIETIC COLONY STIMULATING FACTORS IN LOCALLY ADVANCED (LABC) OR METASTATIC (MBC) BREAST CANCER. A PHASE I-II TRIAL.

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In a phase I-II trial, E and C + G-CSF or GM-CSF were used with different schedules and dose levels (DL) in LABC and MBC. Scheduling was: (a) EC+G-CSF and EC+GM-CSF, with EC in combination q3w x4; (b) E/C+GM-CSF, with E and C alternating q2w x6; (c) E→C+G-CSF, with E given q2w x3 followed by C q2w x3. Treatment duration, total drug dose and planned dose-intensity were equal for the 3 schedules for each planned DL. Planned DL (mg/sqm) for E and C were, respectively: (a) EC, level I, 75 and 1500; level II, 82.5 and 2250; level III, 90 and 3000; (b) E/C and E→C, level I, 100 and 2000; level II, 110 and 3000; level III, 120 and 4000. G-CSF or GM-CSF, 5μg/kg, were given SC from day 5 and stopped two days before next cycle. 3 pts were planned for each schedule and DL. At level I, all cycles were given on planned time, except one. Ratio required:planned hospitalization days has been 1.6 (97/60); 6 RBC transfusions have been required. No unacceptable toxicity (UT) has been registered. As of Feb 1993, 40/60 planned cycles have been administered with 12 pts enrolled at level II, without UT. 35/40 cycles have been given on planned time, ratio required:planned hospitalization days being 2.9 (116/40), and 10 RBC transfusions have been required. One cohort (E/C+GM-CSF) has been fully evaluated and has shown no UT. Thus, 3 pts entered level III of the same schedule. Overall, hematologic toxicity has been greater at level II than level I and for the 14-day than 21-day schedule. Among the 17 evaluated pts, response rate has been 82.3% (14/17; 95% C.I. 64-100) with 7 CR (2 pathological in 4 LABC), 7 PR, 2 SD, 1 PD.
[Dr. Carlomagno is a recipient of an A.I.R.C. fellowship]

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PHASE I-II TRIAL OF INTENSIFICATION OF THE MAID REGIMEN WITH LENOGRASTIM (rHuG-CSF) IN PATIENTS (pts) WITH ADVANCED SOFT TISSUE SARCOMA (STS).

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Due to the dose-response relationship found in the chemotherapy of STS, this study was done to assess the maximal tolerated dose level of the MAID association achievable with lenograstim support. Following a first cycle of MAID at conventional dose with either lenograstim or placebo, eligible patients were included to receive this association at successive dose levels (MAID +25%, +45%, +65%, +85%, +100%), with 4 pts per dose level, and a maximum of 4 intensified cycles. Lenograstim, beginning on D4, was given for 10 days by S.C. route at 5 μg/kg/d (level 1) and 10 μg/kg/d for the other levels. No patient could receive more than level 2 (MAIDx1.45). Results are summarised below :

Dose level	*(1) MAID + 25%*		*(1) MAID + 25%*		*(2) MAID + 45%*	
Lenograstim (μg/kg/d)	5		10		10	
N° cycles (N° pts)	15 (4)		14 (4)		15 (8)	
WBC (/mm3) mean nadir/cycle	500	(200-1200)	100	(0-800)	200	(0-1100)
PNN (/mm3) mean nadir/cycle	300	(0-700)	100	(0-300)	200	(200-200)
Days PNN ≤ 500 (median)	3.5	(0-6)	3.0	(3-12)	8	(2-11)
Days PNN ≤ 1000 (median)	5.5	(3-7)	8	(3-17)	9	(4-14)
Days platelets ≤ 20000/mm3	0	(0-2)	1.5	(0-10)	3	(0-7)
Mean duration in days/cycle						
Febrile neutropenia (≥38°C)	1.1	(0-4)	1.5	(0-9)	1.1	(0-7)
Hospitalisation for toxicity	2.2	(0-6)	3.1	(0-14)	6.3	(0-22)
Mucositis (grade 3-4) (% cycles)	7		7		60	

No cumulative toxicity was noted in successive cycles. One death related to therapy occurred (level 1). The median number of cycles was 4 at level 1 and 2 at level 2. Results of relative dose intensity are presented below :

Level 1 (5)			Level 1 (10)			Level 2	
C1-0.967	C2-0.944	C3-0.997	C1-0.935	C2-0834	C3-0.837	C1-0837	C2-0.767

Conclusion : Lenograstim allows 25% dose intensification of standard MAID with no apparent difference between the 2 lenograstim dosages. Grade 4 mucositis was dose-limiting at MAIDx1.45 dose level.