(25 patients). In the latter dose range the FSRT was partially delivered concurrently with the CRT. Concurrent chemotherapy was administered to 47% (41) and neoadjuvant chemotherapy to 4% (3) . Two year actuarial rates of overall survival and disease free survival were 98% and 83%. Local, nodal and distant control rates at 2 years were 86%, 98% and 94%. Two year local control rates by T category were: T1: 95%, T2A: 83%, T2B: 88%, T3:100%, T4: 66%. Means of the maximum point dose to brainstem and optic chiasm were 56% and 34% of the prescribed FSRT dose. FSRT delivered with IMRT allowed larger CTV's to be treated (median volumes: 48 ml IMRT, 38 ml XPlan, 37 ml XKnife) permitting the inclusion of involved retropharyngeal nodes in the volume treated with FSRT. No patients have developed significant late toxicity at the time of this review.

Conclusion: FSRT has been successfully integrated with CRT for the initial management of NPC. Coverage of larger volume tumours was better achieved with stereotactic IMRT than Xknife or XPlan. Sparing of critical normal structures without compromise of dose delivered to the tumour was achieved. A comparison of FSRT to CRT and large volume nonstereotactic IMRT will be presented.

684 ORAL

Radiotherapy combined with cisplatin, carboplatin, mitomycin C, and 5-FU single drug or two drug chemotherapy compared to radiotherapy alone in unresectable head and neck cancer - a meta-analysis

W. Budach[1], T. Hehr[1], C. Belka[1], K. Dietz[2]. [1] *University Hospital Tuebingen, Radiation Oncology, Tuebingen, Germany;* [2] *University Tuebingen, Institute for Medical Biometry, Tuebingen, Germany*

Background: Former meta-analysis on the addition of chemotherapy to radiotherapy in unresectable squamous cell cancer of the head and neck showed a small but significant survival advantage in favour of simultaneous chemotherapy. However, the meta-analysis included studies with older bleomycin and MTX containing chemotherapies that are not longer considered standard and did not take into account differences in the fractionation schedules used in the studies. Therefore, we performed a meta-analysis based on published data on modern chemotherapeutic regimens in combination with different radiation schedules.

Methods: Randomised trials comparing radiotherapy alone with simultaneous or alternating chemo-radiotherapy using cisplatin, carboplatin, mitomycin C, and 5-FU as single drug or combinations of 5-FU with one of the other drugs were included into the analysis. Group I trials included studies with conventionally fractionated radiotherapy (CF-RT) with or without single drug simultaneous chemotherapy. Group II consisted of trials with CF-RT in combination with or without simultaneous two drug chemotherapies or CF-RT compared to alternating chemo-radiotherapy (two drugs). Group III analysed studies of hyperfractionated-accelerated radiotherapy (HFX/AFX-RT) compared to HFX/AFX-RT in combination with simultaneous single or two drug chemotherapy. Survival data were fitted to a log-normal distribution to assess differences in survival in the respective study. The mean difference in overall survival of the pooled data in groups I-III were estimated using a maximum likelihood method.

Results: 20 trials with a total of 3513 patients were included into the analysis. Group I, II, and III consisted of 7, 6, and 7 studies including 1229, 951, and 1333 patients, respectively. Single drug chemotherapy in combination with CF-RT (group I) resulted in a survival benefit of 18.8 months (14.6 - 23.7 months 95% CL) compared with CF-RT ($p<0.00001$). The use of two drug chemotherapy in combination with simultaneous or alternating CF-RT (group II) was associated with an 8.8 months (5.4 - 12.8 months 95% CL) survival advantage compared with CF-RT alone ($p<0.001$). HFX/AFX-RT in combination with single or two drug simultaneous chemotherapy (group III) resulted in a 12.1 months (8.9 - 15.9 months 95% CL) longer survival than HFX/AFX-RT alone ($p<0.0001$).

Conclusions: Cisplatin, carboplatin, mitomycin C, and 5-FU single drug or combinations of 5-FU with one of the other drugs combined with simultaneous radiotherapy leads to a profound survival benefit in unresectable head and neck cancer patients irrespective the fractionation schedule of the radiotherapy.

Symptom management/Quality of life

685 ORAL

A phase 3, randomized, double-blind, placebo-controlled study of darbepoetin alfa in patients (pts) with lymphoproliferative malignancies

M. Hedenus[1], J. San Miguel[2], D. Watson[3], J. Matchum[3], G. Rossi[4], T.J. Littlewood[5]. [1] *Sundsvall Hospital, Department of Medicine, Sundsvall, Sweden;* [2] *Hospital Universitario de Salamanca, Salamanca, Spain;* [3] *Amgen Ltd., Cambridge, UK;* [4] *Amgen Inc., Thousand Oaks, CA, USA;* [5] *Oxford Radcliffe Hospital, Oxford, UK*

Background: Darbepoetin alfa (Aranesp®) is a unique erythropoietic protein that is safe and effective for treatment of chemotherapy-induced anaemia in pts with solid tumors. Results of a phase 2 study suggest that similar outcomes could be achieved in pts with lymphoproliferative malignancies (Hedenus et al, 2002). This confirmatory phase 3 study was designed to evaluate the efficacy and safety of darbepoetin alfa in pts with lymphoproliferative malignancies.

Methods: This multicenter, randomized, double-blind, placebo-controlled study was conducted in anaemic pts (haemoglobin [Hb] $\leq$ 11.0 g/dL) with lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma, or chronic lymphocytic leukaemia) or myeloma who were receiving chemotherapy. No lower limit for Hb concentrations or specific endogenous erythropoietin level requirement was specified at study entry. Pts were required to be red blood cell (RBC) transfusion-free in the 2 weeks before randomization. Pts (n = 349) were randomized to receive darbepoetin alfa 2.25 mcg/kg (n = 176) or placebo (n = 173) by subcutaneous injection once weekly for 12 weeks. Mean change in Hb was calculated by 2 methods: in the intent-to-treat (ITT) analysis, missing values were imputed by last value carried forward; in the completers analysis, missing values were not imputed and only those pts who had a week 13 Hb value were included. Both methods excluded values within 28 days of RBC transfusion.

Results: see table.

The treatment effect of darbepoetin alfa relative to placebo was evident regardless of baseline endogenous erythropoietin level. Efficacy profiles were consistent between pts with lymphoma and myeloma. Improvements in health-related quality of life were also associated with darbepoetin alfa. The overall safety profile of darbepoetin alfa was consistent with that expected for this pt population.

Conclusions: Darbepoetin alfa is well tolerated and effective in increasing haemoglobin and reducing transfusions across a broad population of anaemic pts with lymphoproliferative malignancies.

686 ORAL

Epoetin alfa rapidly increases hemoglobin levels in anemic cancer patients receiving chemotherapy: results from a meta-analysis of nine randomized, placebo-controlled studies

M. Dicato[1], M. Zagari[2]. [1] *Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg;* [2] *Johnson & Johnson Pharmaceutical Services, LLC, Raritan, NJ, USA*

Background: Because of the relatively short duration of chemotherapy, it is important that any concurrently administered anemia treatment affords a clinically meaningful and rapid increase in hemoglobin (Hb) level to assure optimal patient benefits, including preservation or improvement of quality of life (QOL). Results from two large, multicenter, prospective, open-label, non-randomized, community-based studies (Demetri 1998; Gabrilove 2001) in anemic cancer patients undergoing chemotherapy showed mean Hb increases of ~1 g/dL after 1 month and ~2 g/dL after 2 months of epoetin alfa therapy (mean baseline Hb, ~9.4 g/dL).

Methods: To further characterize the Hb response to epoetin alfa, Hb data were gleaned from 1,646 chemotherapy patients who had received epoetin alfa 150-300 IU/kg three times weekly or placebo in nine randomized studies,

Abstract 685 – Table

	Darbepoetin alfa (n=174)	Placebo (n=170)	
Kaplan-Meier Proportion (95% CI) achieving haemoglobin response[a]	60% (52, 68)	18% (12, 24)	<0.001
Kaplan-Meier Proportion (95% CI) achieving haematopoietic response[b]	65% (57,73)	24% (18, 31)	< 0.001
Mean change (SE) in Hb (g/dL) from baseline to end of treatment (ITT analysis)	1.80 (0.17)	0.19 (0.10)	< 0.001
Mean change (SE) in Hb (g/dL) from baseline at 12 weeks (completers analysis)	2.66 (0.20) (n = 94)	0.69 (0.14) (n = 86)	< 0.001
Incidence (95% CI) of RBC transfusions from week 5 to end of treatment	31% (24, 38) (n = 167)	48% (41, 56) (n = 165)	< 0.001

[a] Increase of * 2.0 g/dL from baseline in the absence of RBC transfusions [b] Increase of * 2.0 g/dL from baseline or a haemoglobin value * 12.0 g/dL in the absence of RBC transfusions

and for whom Hb values had been collected at various times between study days -30 and 400. We then retrospectively analyzed estimated Hb values for baseline and Weeks 1, 4, 8, and 10 (Days 0, 7, 28, 56, and 70) for 1,285 of the 1,646 patients who had recorded Hb values for each week from baseline through at least Week 10.

Results: As shown below, mean Hb levels for the 1,285 patients increased from 9.7 g/dL at baseline to 11.5 g/dL by Week 10 in the epoetin alfa treatment group, and from 9.7 g/dL to 9.9 g/dL at the same time point in the placebo group. Comparison of the mean changes in Hb values from baseline to each subsequent study week showed significantly ($P<.001$) greater increases in Hb level for the epoetin alfa group than for the placebo group at each evaluation, beginning at Week 1. In the epoetin alfa group, the Hb response was rapid, with increases of 1.0 g/dL by Week 4 and 1.7 g/dL by Week 8.

Week	Mean Hb Level (g/dL)		Mean Change in Hb Level (g/dL)	
	Epoetin alfa (n = 771)	Placebo (n = 514)	Epoetin alfa (n = 771)	Placebo (n = 514)
Baseline	9.7	9.7	–	–
1	9.8	9.5	0.1*	-0.1
4	10.7	9.7	1.0*	0.0
8	11.4	9.9	1.7*	0.2
10	11.5	9.9	1.8*	0.3

*$P<.001$; epoetin alfa vs placebo, 2-sample *t* test

Conclusion: Results of this meta-analysis confirm those of earlier randomized (Littlewood 2001) and non-randomized studies, indicating that the administration of epoetin alfa to anemic cancer patients undergoing chemotherapy results in a rapid increase in Hb level. These findings are clinically relevant, as maintaining Hb levels around 12 g/dL or higher during chemotherapy can prevent the deterioration in QOL associated with anemia and its sequelae, particularly fatigue.

687 ORAL

The oral NK1 antagonist aprepitant for the prevention of chemotherapy induced nausea and vomiting: pooled data from 2 randomized, double-blind, placebo controlled trials

R. Gralla[1], P. Hesketh[2], S. Grunberg[3], D. Warr[4], F. Roila[5], S. Chawla[6], A. Carides[7], K. Beck[7], F. Lawson[7], K. Horgan[7]. [1] *New York Lung Cancer Alliance, New York, NY, USA;* [2] *Caritas St. Elizabeth's Medical Center, Brighton, MA, USA;* [3] *University of Vermont, Burlington, VT, USA;* [4] *Princess Margaret Hospital, Toronto, Canada;* [5] *Policlinico Monteluce, Perugia, Italy;* [6] *Century City Hospital, Los Angeles, CA, USA;* [7] *Merck Research Laboratories, West Point, PA, USA*

Background: In each of 2 randomized, double-blind Phase III studies of identical design, the novel NK antagonist aprepitant was shown to enhance the efficacy of standard antiemetic therapy (a 5-HT antagonist plus a corticosteroid) for prevention of cisplatin induced nausea and vomiting. Data were pooled from the 2 studies to obtain more precise estimates of treatment effects with aprepitant.

Methods: Approximately 1040 patients receiving their first cisplatin (* 70mg/m^2) took either standard therapy (ondansetron [O] 32 mg i.v. and dexamethasone [D] 20 mg p.o. on day 1; D 8 mg twice daily on days 2-4) or an aprepitant (A) regimen (A 125 mg p.o. plus O 32 mg and D 12 mg on day 1, A 80 mg and D 8 mg once daily on days 2-3, and D 8 mg on day 4). Rescue therapy was permitted for established nausea or vomiting. Patients rated nausea daily on a 100-mm visual analogue scale (VAS). The primary endpoint was complete response (no emesis and no rescue therapy) for the combined analyses of efficacy, which were prespecified for the acute phase (0-24 h post cisplatin) and post hoc for the delayed phase (24-120 h) and overall study period (0-120 h). A post hoc analysis of nausea scores was also performed using endpoints of no nausea (VAS peak score <5mm) and no significant nausea (VAS peak score <25mm) for the overall 5-day study period. Data were captured in patient diaries and analyzed by a modified intent-to-treat approach. Treatment comparisons were made using logistic regression. Tolerability was assessed by adverse events and physical/laboratory tests.

Results: Patient baseline characteristics were similar between groups. The percentages of patients with complete response in the acute phase (0-24 h) were significantly higher with the aprepitant regimen versus standard therapy (86.0% v 73.2%; $p<0.001$). Similar superiority was observed for the aprepitant regimen in the delayed phase (25-120 h) (71.5% v 51.2%; $p<0.001$) and for the overall 5-day study period (67.7% vs. 47.8%; $p<0.001$). Likewise, compared with patients taking standard therapy, significantly higher percentages of patients on the aprepitant regimen had no nausea (48.2% v 41.5%; $p<0.05$) and no significant nausea (72.1% v 64.9%; $p<0.05$) in the overall study period. Similar incidences of adverse events were reported between treatment groups, and the aprepitant regimen was generally well tolerated. Compared with standard therapy alone, addition of aprepitant to standard therapy provided consistently superior and generally well tolerated antiemetic protection throughout the acute and delayed phases, as shown by data pooled from 2 large Phase III trials in patients receiving highly emetogenic chemotherapy.

688 ORAL

Prevention and management of radiation skin reactions: a randomised controlled trial of skin care approaches in patients with breast, head and neck and anorectal cancer

M. Wells[1], G. Raab[2], S. MacBride[3], N. Bell[2], K. MacKinnon[1], A. Munro[1], L. Samuel[4], R.H. MacDougall[5], M. MacMillan[2]. [1] *University of Dundee, School of Nursing and Midwifery - Clinical Researc, Dundee;* [2] *Napier University, Faculty of Health Sciences, Edinburgh;* [3] *Western General Hospitality, NHS Lothian, Edinburgh;* [4] *Aberdeen Royal Infirmary, NHS Grampian, Aberdeen;* [5] *St. Andrews University, Faculty of Medicine, St. Andrews, United Kingdom*

Background: Although radiation-induced skin reactions are common, there is little evidence upon which to base their management. Previous, small-scale, studies had suggested that sucralfate cream and hydrogels might be effective in the management of skin reactions during and after radiotherapy. We therefore performed a randomised trial on 357 patients to investigate these claims.

Methods: Patients were randomised to apply aqueous cream, sucralfate cream or no cream from the start of radiotherapy, and were supplied with either dry dressings or hydrogel (Intrasite®) dressings (according to their randomised group) for use in the event of moist desquamation. All patients were encouraged to wash with mild soap and water and were given consistent skin care instructions. Skin reactions were assessed weekly using a modified RTOG score and erythema was measured objectively using reflectance spectrophotometry. Patients completed a daily diary card assessing pain, itching, burning, sleep disturbance and skin appearance. Weekly quality of life scores were obtained using the Dermatology Life Quality Index (DLQI). A cost minimisation approach was used to compare the costs of all skin care approaches.

Results: No consistent differences were found in the severity of skin reactions or levels of discomfort suffered by patients in each of the 3 groups. Neither of the preventative' creams conferred any benefit. Patients who smoked were significantly more likely to develop skin reactions than non-smokers. Patients who were randomised to hydrogel dressings took longer to heal than those who applied dry dressings.

Conclusions: There is no evidence to support the prophylactic application of either of the creams tested for the prevention of radiation skin reactions. Dry dressings appear to be at least as effective as hydrogel dressings in the management of moist desquamation. This study, the largest randomised trial of skin care in radiotherapy so far, has generated detailed data (both subjective and objective) on acute radiation skin reactions.

689 ORAL

Nutrition & patient outcomes: prospective randomised controlled trial in head-neck cancer patients undergoing radiotherapy

P. Ravasco[1], I. Monteiro Grillo[2,1], P. Marques Vidal[1], M. Camilo[1]. [1] *Faculty of Medicine, University of Lisbon, Centre of Nutrition and Metabolism (IMM), Lisbon, Portugal;* [2] *Santa Maria Hospital, Radiotherapy Department, Lisbon, Portugal*

Rationale: In a prospective randomised controlled trial we have shown that nutrition intervention significantly increases oral intake. We further investigated whether nutritional counselling or commercial supplements affected predefined patients' outcomes: nutritional status & Quality of Life (QoL).

Methods: Sample size was determined for 85% power, 1% significance. There were 75 head-neck cancer outpatients (pts) stratified by cancer staging: 25 (G1) received individualised nutritional counselling with foodstuffs, 25 (G2) high protein liquid supplements and 25 (G3) an *ad lib* intake. Compliance was weekly monitored. Nutritional status (Ottery's Subjective Global Assessment) and QoL (EORTC) were evaluated at the onset, at the end and 3 months after radiotherapy (RT). ANOVA stratified by stage and adjusted for symptoms and disease outcome was used for comparisons.

Results: At baseline, malnutrition was observed in 56% stage III/IV and 4% I/II pts, p=0.004. During RT, nutritional deterioration occurred in 29%