cultures and squamous carcinoma cell lines; mild synergy between cisplatin and imatinib was found in two of three cell lines as well as in ACC culture. Consequently we chose imatinib with cisplatin for a phase II study in patients with recurrent and/or metastatic ACC.
Material and methods: 18 patients (aged 29–77) with advanced ACC have entered the study. Imatinib was used alone in an initial dose of 800 mg daily for two months with response assessed using both FDG-PET and conventional imaging. Patients then received a combination of imatinib at a reduced dose with cisplatin 80 mg/m^2 at monthly intervals. Depending on responses and toxicity, patients then continued on maintenance imatinib.
Results: of 17 evaluable patients, two developed progressive disease on imatinib alone and left the study. 3 patients have shown a partial response with imatinib and cisplatin with 1 of these 3 on maintenance imatinib, without progression 27 months after commencement. 12 patients had stable disease on cisplatin plus imatinib but 9 of these have progressed since discontinuation of cisplatin and have stopped imatinib. Toxicity from the imatinib-cisplatin combination (median 5 cycles) included one grade 4 thrombocytopenia, one grade 3 anaemia and three grade 3 neutropenia. Non-haematological toxicities included one grade 3 hyponatraemia, four grade 3 fatigue and one grade 3 oedema. After a median follow-up period of 18 months for the 17 patients, 4 have died with progressive disease.
Conclusion: The combination of imatinib (400 mg daily) and cisplatin (80 mg/m^2) appears to be effective in stabilising the disease but this response is maintained in only a minority of patients. FDG-PET proved useful in assessing early response.

1016 POSTER

A new model for concurrent chemoradiation in advanced oropharyngeal cancer: an Indian experience

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Accelerated repopulation (Acc.rep) of tumour cells and repair of sub lethal and potentially lethal damage are the major cause of treatment failure in head & neck cancers. Most successful attempt so far to overcome this problem is concomitant chemoradiation. In spite of impressive gain in local control and disease free survival (DFS), unfortunately this benefit is enjoyed at the cost of increased acute toxicity. The objective of the present model was to utilize the differential between the onset of Acc. rep of tumour clonogens and that of early reacting normal tissue (4 weeks vs. 2 weeks) and thus to minimize acute toxicity. It incorporates concom. chemotherapy only after Acc.rep of early reacting normal tissue is already set in (i.e. 3rd week of radiation) to avoid mucositis. At the same time radiotherapy schedule was so designed that Acc.rep of tumour cells is taken care of by sequencing conventional fractionation (till 3rd week) with twice daily fractionation from 4th week onwards (i.e. Late Hyper fractionation).
Material and Methods: It is a prospective randomized 2-arm study.
Control arm received conven. radiotherapy (64 Gy/32 F: *BED 15 = 57.7*) with weekly cisplatin (30 mg/sq. M) from week 1 to week 6.
Study arm includes **late** hyperfracionated radiotherapy (30 Gy/15 F/3weeks *followed without split* by 120 cGy/F X 2 F daily, 6 hours apart,5 days a week for another 40.8 Gy (TD=70.8 Gy: *BED 15 = 63.26*) combined with weekly cisplatin (30 mg/sq. M) from week 3 to week 6.
From April 2001 to Feb 2003 total 228 patients with stage III/IV oropharyngeal sq. cell cancer were enrolled (after taking informed consent) – 113 in control and 115 in study arm.
Study end points were acute effect, late effect, tumour control and DFS. Median F.U was 28 months till August, 2004.
Summary of Result: Overall response rate at 6 months and DFS at 2 year were 66% & 48% in control arm vs. 70% & 50.6% in study arm ($p > 0.05$). Acute toxicity of skin and mucosa are furnished in the table.

	Grade I	Grade II	Grade III	Grade IV	P value (III+IV)
Acute Mucositis					
Control arm (N = 113)	Nil	87	21	5	<0.001
Study arm (N = 115)	10	101	4	Nil	
Acute Skin Toxicity					
	Grade I	Grade II	Grade III	Grade IV	P value (III+IV)
Control arm (N = 113)	Nil	98	14	1	<0.001
Study arm (N = 115)	8	107	Nil	Nil	

Apart from significantly less mucositis and skin toxicity in study arm, onset of mucositis was also delayed: median onset of grade 2 mucositis was 22 days in control group vs.34 days in study group.
Late toxicity (evaluated as per LENT SOMA score) of both skin and mucosa were comparable in both arms – none had Grade 3 or 4 toxicity in either arm.
Conclusion: This novel concomitant chemoradiation model, theoretically based on our present radio- and chemo-biological knowledge, was found to be able to retain the results of conventional concomitant chemoradiation so far as tumour response and DFS are concerned, with significantly less acute toxicity (both skin & mucosa), comparable late toxicity and so likely to have better patient compliance.

1017 POSTER

Neoadjuvant chemotherapy and concomitant chemo-radiotherapy with accelerated fractionation schedule in advanced carcinoma of the head and neck

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Background: Locoregionally advanced head and neck cancer is a challanging condition to confront with for oncologists. Treatment results with conventional approach (surgery and radiotherapy) are suboptimal. Combined chemo-radiotherapy or accelerated hyperfractionated radiotherapy have been proposed as treatment alternatives. We analyze toxicity, locoregional control rates and survival for advanced head and neck cancer, treated with neoadjuvant chemotherapy (CT) and concomitant chemo-radiotherapy with accelerated fractionation schedule.
Methods and Materials: In a prospective study, from 1999 to 2004, combined chemo-radiotherapy treatment was used in 68 pts (males 62, mean age 55.4 yrs old). Sites of origin were oropharynx 18 (26.5%), larynx 16 (23.5%), hypopharynx 15 (22.1%), oral cavity 14 (20.6%), unknown 3 (4.4%), paranasal sinus 1, and nasopharynx 1. Tumors were classified as UICC TNM stage IV 54 (79.4%), stage III 12 (17.6%), stage I-II 2 (3%). Neoadjunvant CT consisted of two cycles of cisplatin and 5-fluoruracil (CDDP 100 mg/sqm, day 1; 5-FU 1,000 mg/sqm iv, days 1–5 every 28 days). Concomitant CT consisted of weekly cisplatin (25 mg/sqm iv). 72 Gy in 42 fractions, 5 days a week, BID in the last 12 days of irradiation, were intended to be administered in 6 weeks. The mean RT treatment time was 45 days. Surgery as part of the primary treatment was attempted for biopsy-proven residual tumor at the primary site or clinical/radiological residual lymph nodes in the neck. Surgical rescue after tumor recurrence was attempted in 11 pts.
Results: Grade $\geqslant$3 mucositis was recorded in 53 pts (84.2%). Enteral nutrition through nasogastric-feeding tube or percutaneous gastrostomy tube was required in 21 pts (30.9%). Mortality rate attributable to treatment was 7.7% (3.8% acute and 3.8% chronic). The 5-year locoregional control rate was 77.1% (CI 65.0%-89.2%). The 5-year disease-free survival was 49.4% (CI 36.0%-62.8%). The 5-year overall survival was 43.5% (CI 29.3%-57.7%). In multivariate analysis, complete response after primary treatment was the only independent factor for survival.
Conclusions: In our study, the tumor response after combined treatment was the only independent factor for survival. The benefit in tumor control and survival rates has been obtain at the expense of severe acute and late toxicity. This approach could be offered under intensive supportive care to a selected population of patients.

1018 POSTER

A phase II dose escalation study by differential dose allocation to variable target sub-volumes of head and neck (H/N) squamous cell carcinoma (SCCa), using Intensity-Modulated Radiotherapy (IMRT)

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Purpose: We prospectively studied the potential impact of nominal and/or biological effective dose escalation to the tumor by differential dose allocation to different target subvolumes (dose painting) using IMRT. Main endpoints were local control and normal tissue toxicity.
Materials and Methods: Between Dec/2000 and Oct/2003, 33 patients with H/N SCCa (except nasopharynx) were treated by dose painting using IMRT. The GTV plus 5 mm was treated to 67.5 Gy/30 fractions. CTV was divided into CTV1 (GTV plus 1.5 cm margin and the first

echelon lymph node drainage) and CTV2 (residual lymph node regions). A total of 60 Gy/30 fractions was delivered to the periphery of CTV1 and 50–54 Gy/25–30 fractions to the CTV2. Treatments were delivered over six weeks, 5 days/week.
There were 23 stage III/IV, seven stage II and three stage I patients. Nine patients received concomitant, weekly platinum based chemotherapy.
Results: At the time of this analysis, Mar/2005, and a median follow-up of 33.3 months, there were seven locoregional and one distant failures. Three patients died of disease and two of other causes.
The 3-year OS was 90%. The 2 and 3-year DFS was 84 and 73%, respectively. The locoregional control (LRC) was 84 and 78% at two and three years, respectively.
Treatments were well tolerated. Seventeen patients had grade III acute toxicity, 11 patients with mucositis/pharyngitis, and 6 with dermatitis. Grade IV acute toxicity occurred in three patients. Late toxicity was limited to grade I/II in 12 patients. One patient had grade IV laryngeal edema requiring a temporary tracheostomy.
Conclusion: Dose escalation by means of dose painting of the H/N SCCa can safely and effectively be delivered using IMRT. Our preliminary results are encouraging and comparable, if not better, to most randomized dose escalation trials. We believe that, dose painting to escalate the dose needs further evaluation in a randomized fashion.

1019 POSTER

Radiotherapy alone versus radiotherapy with amifostine 3 times a week versus radiotherapy with amifostine 5 times a week: a prospective randomised study in squamous cell head and neck cancer

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Background: Xerostomia is an important side effect of radiotherapy in the head and neck region. To increase the therapeutic index of radiotherapy, it could be worthwhile to enhance selectively the radioresistance of normal tissues. The aim of this study was to investigate whether non-daily (3 times/week) intravenous administration of amifostine, a selective radioprotector, is as effective as daily intravenous administration in reducing the incidence of grade II or higher xerostomia.
Material and methods: 91 patients treated with bilateral irradiation for squamous cell head and neck cancer were randomly assigned to receive radiotherapy alone (AMI-0: 30 patients) versus amifostine 200 mg/m^2 intravenously 3 times/week before irradiation (AMI-3: 31 patients) versus amifostine 200 mg/m^2 intravenously 5 times/week before irradiation (AMI-5: 30 patients). Acute and late xerostomia according to RTOG criteria and quality of life (QoL; EORTC QLQ-C30 and QLQ-H&N35) were assessed at baseline, 6 weeks, 6, 12, 18 and 24 months.
Results: Grade $\geqslant$2 late xerostomia according to the RTOG-criteria differed significantly at 6 months, but not after longer time intervals (AMI-0 74% vs. AMI-3 67% vs. AMI-5 52%, ($p = 0.03$)). No significant differences between treatment arms were found for acute xerostomia or acute mucosal toxicity. During follow up, patient-rated xerostomia was significantly worse among the AMI-0 cases (mean difference score (MDS) 52) compared to AMI-3 (MDS 25) and AMI-5 cases (MDS 29)($p = 0.01$). No significant differences were observed for other QoL dimensions. The 2-year locoregional control rate was comparable for all study arms (AMI-0: 79% vs. AMI-3: 67% vs. AMI-5: 83% ($p = 0.31$)) as was the 2-year overall survival (AMI-0: 70%; AMI-3: 58% and AMI-5 84% ($p = 0.26$)). The most frequently reported side effect of amifostine was nausea and vomiting, which was however mild in most cases, i.e. grade 2 or more toxicity was observed in only 4 patients. However, 28% of the patients discontinued amifostine administration before the end of radiotherapy, mostly because of nausea and vomiting.
Conclusions: In this prospective randomised study, patient-rated xerostomia was significantly less among patients that received amifostine. No difference was noted between amifostine 3 times/week as compared to daily administration. For late xerostomia according to the RTOG criteria, a temporary effect was noted at 6 months, which disappeared thereafter.

1020 POSTER

Squamous cell carcinoma of buccal mucosa treated with free-flap based radical surgery and neck dissection

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Background: To analyze the survival and prognostic factors for survival in patients with squamous cell carcinoma of the buccal mucosa (BSCC) treated with free-flap based radical surgery and neck dissection.
Methods: Between February 1996 to July 2002, 161 consecutive untreated BSCC patients who received free-flap based radical surgery were enrolled. In all, 108 (67%) had advanced BSCC (pathologic stage [pS] III and IV). Most patients (154; 96%) had neck dissection (ND), and 41% of these had pathologic neck node metastases. Post-operative radiation therapy (RT) was scheduled for those who had at least one pathologic finding (i.e., pT4 or nodal positive, or margin $\leqslant$4 mm). Adjuvant concomitant chemo-radiotherapy (CCRT) was given in patients with extra-capsular spreading (ECS).
Results: The 5-year local, local regional control, overall, disease–free, and disease-specific survivals were 85%, 76%, 68%, 69%, and 76%, respectively. The 5-year overall survival was 100% in pathologic stage I, 78% in stage II, 69% in stage III, and 56% in stage IV ($p = 0.033$). The 5-year disease specific survival (DSS) was 100%, 86%, 76%, and 64% in pS I, II, III and IV, respectively ($P = 0.01$). By multivariate analyses, the independent risk factors for local regional control and DSS were pathologic nodal status and differentiation. Pathologic nodal status and pathological overall stage were significant prognostic factors of local control.
Conclusions: Good tumor control and survival can be observed in most patients treated with free-flap based radical surgery and neck dissection.

1021 POSTER

Comparison of Cumulative Incidence (CI) and Kaplan-Meier (KM) estimates on late normal tissue outcome in the presence of competing risks: Evidence from CHART (Continuous Hyperfractionated Accelerated Radiotherapy) Head and Neck Study

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Background: Cumulative incidence (CI) and the Kaplan-Meier (KM) estimates are the two estimators used to quantify the late side effects over time in the presence of competing risks. The aim of this study was to estimate and compare the properties of the two estimators for late morbidity over time for different prognostic groups.
Material and Methods: Three late morbidity endpoints were studied, dryness of the mouth, laryngeal oedema and subcutaneous fibrosis. In each patient, the time to first failure was recorded, or, in patients without any of the events, the time of the last follow up was used as input data for the analysis. KM analysis was performed in two ways: (1) KM (1st) estimate: For each patient the type of first event and time to first event were used as input data. (2) KM (any) estimate: For each patient the event of interest whether it was the first event or not was used as input data. KM (1st) and KM (any) and CI estimates were analysed using SPSS. The estimates were compared in early versus advanced T stage disease among 360 node negative (No) patients in the CHART arm where locoregional failure was the competing event.
Results: The CI estimates were lower for advanced T stage group for all three endpoints when compared to early T stage group. The most striking difference was noticed for dryness of mouth. The CI estimate indicated that there was 9% less dryness of mouth in patients with T3–4 disease. KM (any) rates were very close to KM (1st) rates for the dryness of mouth and the laryngeal oedema endpoints. For subcutaneous fibrosis and oedema rates KM (any) estimate was higher than the KM (1st) estimate and this difference was more pronounced in T3–4 disease. The results are shown at the table below.
Conclusion: Without a comprehensive understanding of the assumptions of KM method, the clinical interpretations must be made with caution. The KM and the CI methods should be used as complementary analyses. The natural behaviour of the tumour site and the competing events under study