1 pt, leiomyosarcoma 1 pt, unknown primary site 1 pt. IL3 was given at a dose of 10 mcg/kg/die s.c. from the onset of G1–G4 thrombocytopenia and continued until recovery. IL3 was given for a mean of 5.7 days (range 2–10) and a median of 5 days. So far 17 out 21 cycles of chemotherapy with thrombocytopenia are evaluable. At present our results are as follows:

- thrombocytopenia G1 (4 cycles): mean increase of platelet counts = 32% within a period of 4.75 days (range 2–10);
- thrombocytopenia G2 (8 cycles): mean increase of platelet counts = 31% within a period of 5.75 days (range 2–10);
- thrombocytopenia G3–4 (5 cycles): mean increase of platelet counts = 157% within a period of 7 days (range 4–10).

The main toxicities were: fever G1–2 8 pts; tremor 3 pts; erythema 1 pts; flu-like symptoms 4 pts; nausea/vomiting G2 1 pts; myalgia G2 6 pts; mental derangement 1 pt.

1 pt, after first administration, has developed acute hypersensitivity with lipothymia.

These data seem to show that IL3 is an active drug in the treatment of thrombocytopenia following a standard dose of chemotherapy. The study is still ongoing and definitive results will be discussed.

255 PUBLICATION

COMPARISON BETWEEN RHGM-CSF AND RHG-CSF ADMINISTERED DURING RADIOTHERAPY AND AFTER PROLONGED CARBOPLATIN INFUSION IN PREVENTING LEUKOPENIA AND MUCOSYTES PRODUCED BY CHEMORADIOTHERAPY IN ADVANCED HEAD AND NECK CANCER

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Concomitant radio-chemotherapy is considered the therapy able to increase the percentage of positive responses in advanced head and neck cancer patients. Nevertheless the related toxicity can become important from the clinical point of view, specially the haematological and mucosa one. In order to reduce the severity of the foreseen haematological and mucosa toxicity, a pilot study with haematological growth factors (G-CSF and GM-CSF) has been performed. Both growth factors were given at the end of the chemotherapy schedule and throughout the radiotherapy programme prosecution. Patients were exposed to infusional chemotherapy for 14 days on end with Carboplatin 30 mg/m^2 and concomitant radiotherapy at the dose of 180 cGy/5 d/w on T and N (*Proc ASCO* 1993, **12:902,**). G and GM were given at the dose of 3 μg/kg starting 24 h since the end of the CBD CA infusion for 14 days. Five patients received G-CSF and 6 patients GM-CSF. All patients gave their informed consent to take part in this pilot study. Results were considered according to the incidence of leukopenia, thrombocytopenia and mucosytes severity, in comparison with a previous group of 28 patients treated with radio-chemotherapy (5th International Congress on Anticancer Chemotherapy, Paris, 0–536, 1995).

		GM	G	Control
Mean peak value	WBC	11.630 (9.390–14.400)	22.146 (6.150–31.400)	
Mean nadir value	WBC	2.473	3.012	2.010 (median 1.921)
	Neutropils	1.379	2.254	1.051 (median 943)
	Platelets	76.900	91.460	80.400 (median 74.000)
Mean day to nadir				
	WBC/Neutr.	45	37	40
	Platelets	35	27	32
Mucosytes grade	1	4/6 (67%)	1/5 (20%)	35.7%
	2	2/6 (33%)	2/5 (40%)	50%
	3	0	2/5 (40%)	14.3%

In conclusion these preliminary data show that both GM and G slightly reduce the severity of Leukopenia but GM-CSF delays the nadir mean day. Moreover GM-CSF, given during radiotherapy remarkably reduces the severity of mucosytes in comparison both with the G-CSF and the historical group. These data are very encouraging and support the elaboration of a further and larger clinical trial in order to confirm the important clinical role of GM-CSF in preventing patients, subjected to a radiochemotherapy programme, from the arising of mucosytes problems.

Nervous system tumours in adults and children

256 ORAL

CHEMOTHERAPY WITHOUT IRRADIATION (RT) IN MEDULLOBLASTOMA PATIENTS YOUNGER THAN THREE. A PROSPECTIVE STUDY BY THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY (SFOP)

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The prognosis of medulloblastoma/PNET of the posterior fossa (PF) in very young children is poor. Survival rate is usually lower than in older children and the quality of life is of particular concern because of the damaging effects of RT on the developing brain. Since 1990, we have been using a post-operative chemotherapy (CT) protocol without RT. The CT regimen included 7 cycles of carboplatin, procarbazine, etoposide, cisplatin, vincristin, cyclophosphamide for 16 to 18 months. In case of progressive disease or relapse under or after conventional CT, salvage treatment including busulfan and thiotepa with bone marrow rescue followed by 50 gy on PF alone was recommended. Thirty-five children <3 yr (median, 16 m) entered this study. Twelve of 35 patients (pts) with no measurable disease after surgery were considered as low risk pts (LR), and 23 with local residue or metastasis as high risk pts (HR). Among the 12 LR pts, 8 are in CR1 with a median follow-up of 30 m (11 to 54 m). Four out of twelve experienced local relapse. Three of them are in CR2 after salvage treatment along with surgery (2 pts), 10 m$^+$, 18 m$^+$ and 30 m$^+$ after relapse. The last pt died without further therapy. Among the 23 HR pts, only 2 achieved CR with conventional CT (17 and 34 m$^+$), 10 relapsed 1 to 19 m after surgery, 11 had progressive disease 1 to 17 m under CT. The 3-yr DFS for LR and HR pts was 67% and 6.5%, respectively (overall DFS, 27%). The 3-yr overall survival for LR and HR pts was 92% and 28% respectively. This protocol appears efficient in LR pts. Another strategy needs to be designed for HR pts. **Supported by ARC, FRANCE.**

257 ORAL

RADIATION THERAPY (RT) IN THE MANAGEMENT OF CRANIOPHARYNGIOMA

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This is a review of 37 children and adolescents treated by RT at IGR between January 1969 and December 1992. Maximum follow-up is 22 years. Mean age is 6.4 years (range 1–15) and the M/F sex ratio is 0.76. RT was applied in the initial management, alone or following a surgical procedure, in 18 cases (49%). In the remaining 19 patients, surgery was used as initial single modality and repeated in 13 of them. In these cases, external RT was considered at the time of a further relapse only. In 2 patients, an intra cystic radiocolloid administration (Re 106) was also employed. External RT delivered 45 to 55 Gy using Megavoltage equipment (Co 60: 15, 5–25 MV, X-rays: 22) in 3 to 5 daily sessions of 1.8 to 3.3 Gy. At the time of analysis, 8 children (22%) presented with a local failure. All were observed in children in which RT had been initiated at the time of relapse, and none if RT had been applied in the initial course ($P < 0.01$). All failures were located in the target volume. Nine patients died: 7/9 died from tumor progression, 1/9 from second malignancy and 1/9 from brain injury. Five and 10 years survival are 89 and 67%. Two

major complications were recorded: a bilateral blindness 2 years following the administration of 55 Gy (2 Gy per fraction) in a 14 year-old girl; a bitemporal glioblastoma 9 years following the administration of 50 Gy in a 1 year-old girl. All patients required GH and thyroid hormone replacements and the endocrinological condition deteriorated in 12. Severe psychological disturbances recorded in 11. RT administered to a dose of 45–55 Gy provide an excellent and durable local control when administered early in the course of disease.

258 ORAL

A PHASE III MULTI-INSTITUTIONAL RANDOMISED TRIAL OF LONIDAMINE (L) AND POST-OPERATIVE RADIOTHERAPY (RT) IN SUPRATENTORIAL MALIGNANT GLIOMA

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Lonidamine, an indazole carboxylic acid derivative, was reported in Phase II/III trials to have efficacy as radiopotentiator in malignant glioma.

Between October 1990 and August 1994, 191 pts. with supratentorial malignant glioma were randomly allocated to treatment with RT or RT + L, following surgical resection. Prior to randomisation patients were stratified according to age. One patient was ineligible and excluded from the study (not malignant glioma).

Patients (pts) in arm A (98 pts) received RT alone (50 Gy whole brain plus 14 Gy coned-down boost to the tumour volume, 2 Gy/day for 5 days a week), those in arm B (92 pts) received RT + L (150 mg 3 times daily for 1 year starting from 3 days before irradiation). The groups were comparable in median age, performance status, TNM classes, sex, residual tumour size after surgery and histologic grade. Median follow up was 49 weeks. Intention to treat analysis failed to demonstrate significance difference in the survival rates and shapes of the survival curves between the two treatment arms.

Cumulative survival at 12 and 24 months calculated by the Kaplan-Meier method were 50% ± 5% and 13.4% ± 4% for arm A, 49% ± 5% and 13.4% ± 4% for arm B. ($P > 0.4$). The Cox proportional hazards model confirmed the prognostic variables of age ($P < 0.002$), Karnofsky performance status ($P < 0.02$) and histologic grade ($P < 0.03$). No subgroup examined demonstrated a survival or response advantage for the combination arm. Both acute and late radiation reactions were similar in the two groups. This trial fails to substantiate therapeutic synergy of RT + Lonidamine with this dosage and schedule in the postoperative radiotherapy of malignant glioma.

259 ORAL

RADIOTHERAPY FOR GRADE II GLIOMAS

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From 1980–1991, 164 patients with a WHO-grade II astrocytoma received radiotherapy following surgery at UCSF. All patients had CT or MRI for diagnosis and/or treatment planning. Radiation doses were above 50 Gy in most patients, usually 54 Gy or 59.4 Gy. The 5- and 10-year overall survival rates were 79% and 67%, respectively; the median survival was 12.9 years. In the multivariate analysis, KPS, histology and duration of symptoms were significant. Age, location, surgical extent, or radiation dose were not significant. The 5-year survival rates for patients with KPS $\leq$ 70 and KPS > 70 were 60% and 87%, respectively. The 5-year survival rates for the different histologies were 95% for (mixed) oligodendroglial, 78% for ordinary, and 57% for gemistocytic astrocytomas. The 5-year survival rates for patients with a duration of symptoms $\leq$2 months versus >2 months were 65% and 83%. Progression free survival rates at 2-, 5- and 10-years were 77%, 68% and 50% respectively. In predicting progression free survival, only KPS was significant. Histology was important in predicting the survival following progression, with a 5-year survival of 83% in recurrent (mixed) oligodendroglial versus 33% in recurrent ordinary astrocytoma.

260 ORAL

HIGH-DOSE CHEMOTHERAPY (HDC) FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN PLACE OF CRANIOSPINAL IRRADIATION (RXT) IN YOUNG CHILDREN TREATED FOR MEDULLOBLASTOMA (MB)?

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Cranio-spinal RxT is the standard prophylaxy in MB but, because of its late effects, children under 3 years of age are currently treated with conventional chemotherapy in order to delete or even avoid RxT. Among these patients treated without RxT in the SFOP study, 20 relapsed under conventional chemotherapy and entered a study of HDC followed by ABMT. Their median age at diagnosis was 23 m (R5-71) and the relapse occurred at a median time of 6.3 m (±5 m) after initiation of chemotherapy. A complete surgery of local relapse was performed in 4/20 and these patients were not evaluable for response. Sixteen out of twenty had measurable disease at primary site (9 pts) at metastatic sites (3 pts) or both (4 pts). Conditioning regimen consisted of combination Busulfan 600 mg/m^2 over 4 days and Thiotepa 900 mg/m^2 over 3 days. After recovery of aplasia, pts with local relapse received local RxT limited to posterior fossa. Among the 16 pts with measurable disease, following HDC, 6 CR, 6 PR, 3 NR, 1 NE were observed (Response rate 75%). For the 20 pts, EFS is 60% with a median follow up of 9 m post BMT (R3-65). Nine pts with localized relapse are alive NED without craniospinal RxT. Toxicity was high but manageable. One complication related death occurred 1 m post BMT. In conclusion: with a 75% response rate, this HDC proved to be very efficient in relapsed MB. A longer follow up is necessary to demonstrate whether, after local relapse, HDC could replace craniospinal RxT as prophylaxis of CNS metastases.

261 ORAL

DOSIMETRIC CONSIDERATIONS IN THE OUTCOME OF MEDULLOBLASTOMA

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Seventy-three patients aged 2 to 48 years were treated for medulloblastoma (MB). Chang staging was: 7% T1, 42% T2, 16% T3a, 27% T3b, 8% T4. Thirty-three percent of patients had spinal axis (SAX) staging. Median radiation doses were posterior fossa (PF) 52 Gy, whole brain (WB) 40 Gy, and SAX 35 Gy. Fraction sizes ranged 0.5–3 Gy (median 1.7 Gy WB, 1.7 Gy SAX, 1.8 Gy PF).

The 5-year overall and disease-free survival are 67% and 59%, respectively. PF control was better for patients receiving >50 Gy to the PF (86% vs 42%, $P = 0.0007$). PF dose >50 Gy gave improved actuarial and disease-free survival. PF control was improved when patients were treated with fraction $\geq$1.7 Gy/day to the brain and spine (84% vs 51%, $P = 0.0006$). When PF was controlled, neuroaxis control was better if >30 Gy to the SAX (97% vs 71%, $P = 0.05$). WB dose did not have an impact on neuroaxis control, but few patients received $\leq$30 Gy WB. Incidence of extra-CNS metastases is 13% and 20% at 5 and 10 years, respectively. Patients with continuous PF and neuroaxis control have an extra-CNS relapse rate of 10%.

Our data confirm a dose response >50 Gy for PF control in MB. SAX dose of >30 Gy is necessary for neuroaxis control. Fraction size >1.7 Gy appears to improve local control. Ten percent of patients develop extra-CNS metastases despite CNS control.

262 ORAL

LOW EXPRESSION OF PLASMINOGEN ACTIVATOR INHIBITOR (PAI) TYPE I (PAI1) AND HIGH LEVEL OF PAI TYPE 2 (PAI2) ARE ASSOCIATED TO A BETTER OUTCOME IN GLIOMAS

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Urokinase-type plasminogen activator (uPA) and PAI1, are involved in invasive phenotype of several tumors, and have been recently described in malignant gliomas. Expression and tissular localization of PAI2, as well as the clinical relevance of these proteases, need however to be investigated. In the present study, 42 patients with glioma were analyzed for expression of uPA, PAI1, and PAI2 (oligodendrocytoma (n = 2), glioma