undergoing lap-assisted anterior resection (but not abdomino-perineal resection) but this is not currently supported by the 3-year disease free survival data.

44 Abstract not received

Scientific Symposium
Brain tumours in childhood – problems and new concepts

45 INVITED

Hyperfractionated radiotherapy for PNET

R.D. Kortmann[1], L. Gandola[2], U. Ricardi[3], R. Taylor[4], C. Carrie[5]. *On behalf of the SIOP Brain Tumour Subcommittee Working Group for PNET.* [1]*Clinic for Radiation Therapy and Radiooncology University of Leipzig, Germany;* [2]*Radiotherapy, Istituto Nazionali dei Tumori, Milan, Italy;* [3]*Radiation Therapy Department, University of Turin, Italy;* [4]*Cookridge Hospital, Leeds, UK;* [5]*Department of Radiotherapy, Centre Leon Berard, Lyon, France.*

Background: In children with standard risk PNET (medulloblastoma) hfx-RT may allow a higher local total dose (68–72 Gy) in order to improve tumour control within the posterior fossa (PF) and reducing long-term toxicity in normal brain compared with conventionally fractionated RT (36 Gy). In high risk PNET hfx-RT (40 Gy CSA/68–72 Gy tumour site) results in increased tumour cell kill without increasing normal tissue toxicity. The rationale for hyperfractionated radiotherapy (hfx-RT) is to try to reduce delayed effects of radiation injury and to prevent tumour repopulation by giving more than one radiation fraction per day in smaller doses per fraction.allowing a redistribution of proliferating tumour cells with some cells entering a radiosensitive stage. Other non-proliferating or dose-limiting tissue, such as normal brain, will potentially be spared.
Methods: Results from retrospective and prospective series and present observations of ongoing phase II trials were analysed.
Results: *In standard risk disease* 5 year PFS was 76 and 79% (Ricardi et al., 1997, Prados et al., 1993). In the recent SFOP study (1.0 Gy bid. 36 Gy CSA/68 Gy tumour) the 3 year PFS was 81% (overall survival 89%) without chemotherapy. No decrease in intelligence was observed in 22 children tested during the first 2 years (Carrie et al., 2005). The SIOP–HIT PNET IV study is currently investigating this concept in a prospective randomized study and compares hfx-RT (1.0 bid./CSA 36 Gy/PF 60 Gy tumour 68 Gy) with conventionally fractionated RT (CSA 23.4 Gy/PF 54 Gy) followed by 8 courses Cisplatin, CCNU, VCR. *In high risk disease* 14 of 15 patients (93%) remained disease free for a median of 68 months (Allen et al., 1997). In the Milan study, hyperfractionated-accelerated RT (1.3 Gy bid. 39 Gy CSI/1.5 Gy bid. 21 Gy PF boost) was delivered to 31 pts (median age 9 yrs) combined with high-dose sequential postoperative CT. 5 yrs PFS, EFS, and OS were 75%, 72%, and 76% respectively. The UKCCSG phase 1study investigates hyperfractionated accelerated RT (HART) with cisplatin, vincristine and CCNU chemotherapy. In the ongoing HIT 2000 study (intensive chx. followed by hfx-RT 1.0 Gy bid. CSA 40 Gy, boost, 60–68 Gy) only 18/110 patients (16.4%) (0–51 months) showed progressive disease. Data on late effects are not yet available.
Conclusion: Hfx-RT is a novel approach to improve tumour control and survival in standard and high risk PNET. Results of phase II studies are promising. In standard risk PNET a preservation of neurocognitive function might be possible. Quality of life as an endpoint is of increasing importance.

46 INVITED

Treatment of PNET in children without radiotherapy

J. Grill[1], D. Ashley[2], D. Walker[3], S. Rutkowski[4]. [1]*Institut Gustave Roussy, Paediatric Department, Villejuif, France;* [2]*Royal Children's Hospital, Paediatric Oncology, Melbourne, Australia;* [3]*Queens Medical Centre, Paediatric Oncology, Nottingham, United Kingdom;* [4]*Children's Hospital, Paeditric Oncology, Wurzburg, Germany*

Young children with medulloblastoma have a dismal prognosis and morbidity is high with standard therapy including craniospinal irradiation (CSI). Two recently published national trials (one from Germany and one from France) have shed some light on the possibility to treat some children without using CSI. To analyse these results, three groups of patients can be defined a priori: R0M0 (no residue, no metastasis), R1M0 (radiological residue only) and RXM+ (presence of metastasis whatever the residue). Despite the use of completely different chemotherapy regimens and salvage strategy, both trials have shown that more than 70% of children with R0M0 disease can be cured without craniospinal irradiation. In the German trial, these results were obtained after an intensive methotrexate-containing chemotherapy while in the French trial two third of the survivors required a salvage regimen with high-dose chemotherapy. Patients with RXM+ and R1M0 diseases have a poorer prognosis when treated with conventional chemotherapy only. In both trials, desmoplasia was an indicator of better prognosis. In addition, in the French trial, a poorer outcome was observed for patients with subtotal resection (ie surgical report indicating microscopic tumor remnants despite the absence of radilogic residue on early postoperative scans). Both trials claimed an improved intellectual outcome albeit different scales were used for neuropsychologic assessment. Concurrent trials still ongoing or recently completed in the USA and in UK seem to have similar results for R0M0 patients with protocols including early posterior fossa irradiation together with conventional chemotherapy.The brain tumor comittees of the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (USA, Canada, Australia) have started the process to build up a common randomized trial in this category of patients (localized medulloblastomas) to compare the different strategy both in terms of survival and in terms of cognitive outcome. The progresses of this endeavour will be presented at this meeting.

47 INVITED

Modern approach to childhood low grade glioma

G. Perilongo. *Neuro-oncology Program, Department of Pediatrics, University Hospital of Padua, Padua, Italy*

The treatment of childhood low grade glioma (LGG), if not amenable to complete resection, quite often is a relevant clinical challenge. LGG in many instances are indeed slow growing tumours, which, if not controlled, can cause severe morbidity and ultimately jeopardize life. Most of the time children bearing an unresectable LGG can be considered affected by a chromic disease, deserving protracted cures. The treatment philosophy, which has dictated the treatment of malignant cancers, has also inspired the therapeutic concepts for managing childhood LGG. However, it is getting more and more evident that different strategies are needed for them. LGG represent a highly heterogeneous group of neoplasm and comprehensive treatment concepts rarely meet the individual patient's needs. After more than 20 years of clinical research it can be stated with confidence that for unresectable, progressive LGG, chemotherapy (CT) represents an effective treatment modality. It delays tumour growth and postpones the use of radiotherapy (RT), thus sparing the deleterious effects of irradiation on a developing brain. However, CT rarely cures LGG and definitively obviates the need of RT or aggressive surgery. Furthermore, little is known on the actual impact of CT on patients' overall health status. Recent progresses in RT delivering techniques, which allow reducing the safety margins, are tempering the concerns related to the use of this treatment modality in children. While waiting for more biological based therapeutic approaches, CT and RT (other than surgery) are the present tools for treating childhood LGG, which seems to be working best if guided by expert and dedicated multidisciplinary neuro-oncology teams

48 INVITED

New approaches for high-grade gliomas

J. Wolff. *M.D. Anderson Cancer Center, Houston, USA*

High grade glioma are characterized by there heterogenic molecular and histological appearence, and their poor prognosis. With the improvement of radiation and with more radical surgery, survival times have increased. In addition, large phase II studies have shown significant but limited survival benefits with chemotherapy in high grade glioma with temozolomide and nitrosurea. However, numerous clinical trials have been published previously with smaller patient numbers and no control groups. A small positive effect could be missed this way resulting in premature rejection of possible beneficial treatment.
Expanding our former database (Hauch 2005), we analyzed the glioma literature 1997 to 2005 in order to compare treatment results. In this database, one record represents a cohort of patients treated in the same way. Various patient cohort characteristics such as median age, and outcome measures such as median overall survival times (mOS), were documented. Patient population factors influencing the outcome of a cohort were analyzed. Based on those, a predicted outcome for each cohort was calculated. The measured outcome was compared with the predicted outcome to calculate the survival gain archived by the treatment, and treatments were ranked according to their survival gain.
24023 patients are reported in 503 cohorts in 362 publications. The male to female ratio was 1.55 to 1. The median age was 45 years, 9% of the studies included children only. The grade IV to grade III ratio was 3.3 to 1. Supratentorial to infratentorial: 7.1 to 1. Newly diagnosed to recurrent tumors: 1.9 to 1. The median overall survival was 14.5 months.

All major treatment modalities surgery, radiation and chemotherapy had significant impact on survival. When ranking studies according to survival gain, the three highest ranking studies were: Danohue 1997 (BCNU + HFRT), Fukushima 2003 (MCNU + TNF-alpha) and Levin 2203 (PCV + DFMO). When grouping studies according to agent groups, nitrosurea rank above temozolomide, which are still above other groups. Numerous novel appraches such as tumorvaccination with dendritic cells, and EGFR tragetted therapies, provide hope for future further improvement. However, none of theses clinical reports rank higher then the cehmotherapeutic studies.
This literature analysis indicates that, nitrosurea and temozolomide as well as DMFO are promising treatments. Patient numbers in clinical trials represent the crucial factor limiting speed to gain knowledge. Novel approaches need to move to clinical trials with higher patient numbers. Multiinstitutional collaborations are necessary to overcome this problem. In pediatrics, these collaborations have to exceed national boarders.

EACR Special session

50 INVITED

Oncogenic Herpesviruses: Understanding the latent–lytic switch

Adrian Whitehouse. *School of Biochemistry and Microbiology, University of Leeds, Leeds, UK*

Kaposi's sarcoma (KS) was first described in 1872 as a rare disseminated sarcoma of the skin. However, widespread human immunodeficiency virus (HIV) infection has since turned KS into an epidemic disease. A key concern is the major epidemic of KS in Africa. KS is now the most common adult tumour reported in parts of Africa. Furthermore, childhood KS in Africa is becoming more common and unlike adults who usually have a slow-growing form of KS, childhood KS is aggressive and rapidly fatal.
The etiological agent of KS, is the most recently identified human tumour virus, Kaposi's sarcoma associated herpesvirus virus (KSHV). Like other herpesviruses, KSHV has two distinct forms of infection, latent persistence and lytic replication. Although, latent persistence of the KSHV genome has been implicated in tumourigenesis, it is evident that lytic replication plays an important part in the pathogenesis and spread of KSHV infection. Therefore, it is essential to study the molecular mechanisms of reactivation and the control of lytic gene expression for a better understanding of KSHV pathogenesis.
Herein, we will describe the characterisation of the KSHV ORF 50 protein. We demonstrate that it is the key protein responsible for reactivation from the latent state and initiating the lytic replication cycle. KSHV ORF 50 is produced as immediate early protein, it autoregulates its own expression and activates transcription of various viral and cellular genes. Moreover, sustained transient expression of ORF 50 in KSHV latently infected cell lines leads to the stimulation of its own expression and consequently viral lytic replication. This implicates the KSHV ORF 50 protein as the molecular switch for reactivation and initiation of the lytic replication cycle. We will also describe a novel KSHV ORF 50–cellular protein interaction. We have shown that HMG-A can directly interact and significantly enhance KSHV ORF 50-mediated transactivation, suggesting it has an important role in KSHV ORF 50-mediated reactivation and the initiation of the lytic replication cycle. These results will lead to a better understanding of the molecular mechanisms of reactivation and the control of lytic gene expression which are implicated in KSHV pathogenesis.

51 INVITED

IGF-1 receptor in cancer: the perfect target, searching the perfect bullet

L. Girnita, A. Girnita, O. Larsson. *Department of Oncology-Pathology, Cellular and Molecular Tumor Pathology, Cancer Center Karolinska, Karolinska Institute, Stockholm, Sweden*

The insulin-like growth factor 1 receptor (IGF-1R) plays an essential role in malignant processes in at least different ways: 1) it is a promoting factor; 2) it is an anti-apoptotic factor; and 3) it is quasi-obligatory for the establishment and maintenance of the malignant phenotype. Several signaling pathways, including MAP kinase pathways and phosphatidylinositol 3-kinase pathway are activated by IGF-1.
Phosphorylation is known as being the central process governing IGF-1R signaling. However, recently we described the involvement of ubiquitination on IGF-1R function. We demonstrated that Mdm2 serves as a ligase in ubiquitination of the IGF-1R and thereby causes its internalization and degradation. A process discovered as the means by which IGF-1R is turned off, quite surprisingly has been found to provide support for signal transduction. This newly signaling mechanism involves two families of proteins Mdm2 and β-arrestins [1–3].
Our results reveal the involvement of ubiquitination in the IGF-1R signaling pathways. A twin function for IGF-1R ubiquitination mediated by MDM2 is demonstrated: internalization and down-regulation of the receptor in conjunction with activation of the IGF-1R signaling pathway.
The vast expression of IGF-1R in neoplastic cells and tissues combined with its crucial roles in cancer cell growth is making this tyrosine receptor an attractive target to combat malignant diseases. A variety of approaches aimed at targeting IGF-1R has been utilized to prove the concept, or are being developed for potential anticancer therapies. Recently, we demonstrated that the cyclolignan PPP inhibited phosphorylation of IGF-1R without interfering with insulin receptor activity, as well as it reduced phosphorylated Akt, caused apoptosis and induced tumour regression in xenografted mice. PPP did not compete with ATP but interfered with phosphorylation in the activation loop of the kinase domain, in which it specifically blocked phosphorylation of the tyrosine (Y) 1136 residue, while sparing the two others (Y1131 and Y1135) [4].
Currently it is well established that IGF-1R is crucial in many physiological processes like growth, differentiation and aging as well as it is an important player in disease development. Particular attention has been paid at its role in cancer and today the IGF-1R is generally regarded as one of the most promising targets for cancer therapy. However, we have to learn how to use it.

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52 INVITED

Role of p27kip1/stathmin interaction in the regulation of cell motility

B. Belletti, M.S. Nicoloso, M. Schiappacassi, S. Berton, F. Lovat, A. Colombatti, G. Baldassarre. *Division of Experimental Oncology 2, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy*

The relationship between cell movements and cell cycle progression is a topic far to be completely clarified. Recent data from several laboratories suggest that some of the cell cycle related proteins, such as Cyclins, CDKs and CKIs (CDK Inhibitors) directly participate also in the regulation of cell movements.
We investigated the role of the CKI $p27^{kip1}$ in the regulation of cell proliferation and motility in cells in contact with the Extracellular Matrix (ECM).
$p27^{kip1}$ (hereafter p27) is a well known cell cycle inhibitory protein that acts by binding and inhibiting the cyclins/CDKs complexes, preferentially targeting the activity of the Cyclin A/CDK2 and Cyclin E/CDK2 complexes in the nucleus of the cells. Exclusion of p27 from the nucleus results in the loss of its cell cycle progression inhibition while its potential role in the cytoplasm has been for long time unexplored.
Our work demonstrates that in mouse fibroblasts and in sarcoma derived cell lines cell-ECM contact induces a rapid translocation of p27 from the nucleus to the cytoplasm. When located in the cytoplasm, p27 is able to inhibit cell migration. This activity of p27 relies in the C-terminal portion of the protein, since a deletion mutant that lacks the last 28 aminoacids fails to inhibit cell motility although retains the ability to inhibit cell cycle progression. Thus, p27 displays two different activities that could be separated by using different deletion mutants. Based on this notion we identified as p27-interactor the Microtubules-destabilizing protein stathmin. We demonstrated that *in vitro* and *in vivo* p27 is able to bind and inhibit the activity of stathmin thus increasing the cellular MT-stability and that this increase was eventually linked to the inhibition of cell migration. High expression of stathmin and low expression of p27 result in enhanced cell migration while high p27 levels in the cytoplasm and low stathmin expression decreased cell motility through different ECM substrates. Accordingly, in a panel of human sarcomas p27/Stathmin cytoplasmic expression is high in primary tumors and low in metastatic diseases.
In conclusion, our work contributes to identify a new function for p27 protein that strictly connects the regulation of cell cycle progression with the modifications of the MTs network, thus providing new insights in the comprehension of tumor progression and metastatization that could eventually results in new therapeutic approaches in the treatment of metastatic cancers.