4101 ORAL

Mammalian target of rapamycin (mTOR) inhibition in acute lymphoblastic leukemia: a promising therapeutic option

R. Crazzolara[1], A. Cisterne[2], M. Thien[2], J. Hewson[2], R. Baraz[2], K. Bradstock[3], L. Bendall[2]. [1]*Medical University of Innsbruck, Pediatrics, Innsbruck, Austria;* [2]*Westmead Millenium Institute, Westmead Institute for Cancer Research, Sydney, Australia;* [3]*Westmead Hospital, Haematology, Sydney, Australia*

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children. Despite advances in the treatment of ALL, a substantial part of children relapse and/or develop serious short and long term complications. Therefore the development of more potent but less toxic drugs will be imperative to save more lives. The mTOR (mammalian target of rapamycin) serine threonine kinase has been shown to be aberrantly activated in many tumors, including hematological malignancies. Since mTOR inhibitors have a potent anti-neoplastic effect and are now being used in clinical trials, we investigated the effects of the orally available mTOR inhibitor, RAD001 (Everolimus), in a NOD/SCID model of human childhood B cell progenitor ALL. RAD001 treatment of established disease increased the median survival of mice from 21.3 days to 42.3 days ($p < 0.02$). RAD001 together with vincristine significantly increased survival compared to either treatment alone ($p < 0.02$). In keeping with *in vitro* data RAD001 induced a cell cycle arrest in the G0/1 phase with associated dephosphorylation of the retinoblastoma protein, and reduced cyclin dependent kinase 4 and 6 levels. Ultrastructure analysis demonstrated the presence of autophagy and limited apoptosis in cells of RAD001 treated animals. In contrast cleaved PARP suggested apoptosis in cells from animals treated with vincristine or the combination of RAD001 and vincristine, but not in those receiving RAD001 alone. In conclusion, we have demonstrated activity of RAD001 in an *in vivo* leukemia model supporting further clinical development of mTOR inhibitors for the treatment of patients with ALL.

4102 ORAL

Preliminary results of intensity modulated radiation therapy for pediatric head-and-neck rhabdomyosarcoma in France

J. Leseur[1], L. Claude[2], J.L. Habrand[3], M.A. Mahe[4], S. Supiot[4], A. Laprie[5], E. Le Prisé[1], G. Truc[6], V. Bernier[7], C. Carrie[2]. [1]*Centre Eugene Marquis, Radiotherapy, Rennes, France;* [2]*Centre Léon Bérard, Radiotherapy, Lyon, France;* [3]*Institut Gustave Roussy, Radiotherapy, Villejuif, France;* [4]*Centre René Gauducheau, Radiotherapy, Nantes, France;* [5]*Centre Claudius Régaud, Radiotherapy, Toulouse, France;* [6]*Centre Centre Georges Francois Leclerc, Radiotherapy, Dijon, France;* [7]*Centre Alexis Vautrin, Radiotherapy, Vandoeuvre les Nancy, France*

Background: In head-and-neck rhabdomyosarcoma (RMS), radiotherapy have an important place in treatment because tumors are rarely available to complete surgical resection. Intensity-modulated-radiotherapy (IMRT) is an advanced technology that allows a better dose homogeneity inside the tumor while sparing normal tissue. The purpose is to evaluate initial clinical results of IMRT for pediatric head-and-neck RMS in France.
Material and Methods: Between January 2003 and December 2008, 27 patients with head-and neck RMS were treated with IMRT in 6 French departments of Radiation Oncology. There were 18 male and 9 female patients, with a median age of 8.9 years at time of irradiation (8 months-20 years). Seventeen patients had a parameningeal primary tumor and 10 orbital. All patients were clinical Group III. Eleven patients had embryonal histologic tumor, 11 alveolar, 1 botryoid and 4 unknown. The mean tumor size was 4.7 cm (2.2−7.1 cm), 45% of tumors measuring >5 cm. Four patients (15%) had nodal involvement at diagnostic. Six patients (22%) had initially metastatic disease: 3 pulmonary, 2 bones and 1 bone marrow. All patients had undergone chemotherapy according to cooperative group RMS protocols. Outcome and toxicities were evaluated in medical records on each cancer center.
Results: Median follow-up was 23.2 months (3−52). The median dose was 50.4 Gy (36−55.8). Among patients with orbit tumors, one failure occurred in reduced fields (10%) and one patient aged of 8 months at diagnostic had progressive disease during treatment (10%) and developed meningeal carcinomatosis. One failure occurred in field (6%) among patients with parameningeal RMS, and one patient developed a marginal failure with synchronous bones metastasis (6%). No failure in regional lymph nodes was observed. Disease-free survival at 4 years were 93%, and 78% for parameningeal RMS and for orbital RMS, respectively. Overall survival at 4 years were 87%, and 89% for parameningeal RMS and for orbital RMS, respectively. Radiation Therapy Oncology Group acute mucosal toxicity grade 3 concerned 2 patients and one patient presented a corneal ulcer. No patient developed acute toxicity Grade 4 or 5. Late toxicities observed to date were 3 keratitis, 2 trismus and 1 hypothyroidism. No secondary solid tumor was observed at last follow-up visit.
Conclusions: Our initial clinical results of IMRT for pediatric head-and-neck RMS revealed a good disease-free-survival rate, especially for parameningeal-RMS. Long-term-follow-up is needed to evaluate late toxicities.

4103 ORAL

Phase I study of temozolomide combined with oral etoposide in children with recurrent or progressive medulloblastoma

A. Ruggiero[1], D. Rizzo[1], G. Attinà[1], I. Lazzareschi[1], P. Maurizi[1], S. Mastrangelo[1], R. Migliorati[2], P. Bertolini[3], M. Pastore[4], R. Riccardi[1]. [1]*"A. Gemelli" Hospital UCSC, Department of Pediatric Oncology, Roma, Italy;* [2]*Pausilipon Children's Hospital, Department of Pediatric Oncology, naples, Italy;* [3]*Parma University, Department of Pediatric Oncology, Parma, Italy;* [4]*"Casa Sollievo della Sofferenza", Department of Pediatric Oncology, San Giovanni Rotondo, Italy*

Background: The prognosis of recurrent or progressive medulloblastoma (MB) is still poor. This study was designed to investigate the potential therapeutic benefit of combination therapy with Temozolomide (TMZ) and oral Etoposide (VP16) in children with progressive or relapsed MB. A phase I trial was conducted to establish the toxicity and maximum tolerated dose (MTD) of this orally administered combination.
Methods: The combination therapy with TMZ and oral VP16 once daily was investigated in cohorts of 3 to 6 patients by escalating either the dose of TMZ or number of days of VP16 treatment given at a fixed dose. Cohorts of patients were enrolled at 4 different levels:
1. TMZ 120 mg/m^2 on days 1−5 and VP-16 50 mg/m^2 on days 1−8;
2. TMZ 150 mg/m^2 on days 1−5 and VP-16 50 mg/m^2 on days 1−8;
3. TMZ 150 mg/m^2 on days 1−5 and VP-16 50 mg/m^2 on days 1−10;
4. TMZ 150 mg/m^2 on days 1−5 and VP-16 50 mg/m^2 on days 1−12.

Cycles were repeated every 28 days. Intrapatient dose escalating was not permitted. A total of 66 courses were administered to 14 patients with a median median age of 5.7 years. All 14 patients had received craniospinal radiotherapy and prior chemotherapy, including high dose chemotherapy. Given the risk of infection by Pneumocystis carinii all children received prophylaxis with cotrimoxazole. Patients with an objective response continued chemotherapy untill progression disease or dose-limiting toxicity (DLT).
Results: None of the 3 patients at dose level 1 and 2 had DLT. One patient at dose level 3 had grade III/IV thrombocytopenia, anemia and neutropenia. Therefore, 3 additional patients were added and no DLT were registered. At dose level 4, a grade 4 thrombocytopenia and neutropenia were observed in the first two patients enrolled. Therefore, the MTD was established at dose level 3.

DLT by Dose Level

Dose Level	TMZ dose (mg/m^2/d)	VP-16 dose (mg/m^2/d)	Patients	DLT
1	120×5 days	50×8 days	3	0
2	150×5 days	50×8 days	3	0
3	150×5 days	50×10 days	6	1
4	150×5 days	50×12 days	2	2

Although response to therapy was not a primary outcome of the trial, 12 patients were evaluable for response. One patient had a partial response, another patient a complete response, 7 patients stable disease, and 3 progressive disease; 2 were not evaluable for response.
Conclusion: The recommended phase II dose in children is TMZ 150 mg/m^2 on days 1−5 and VP-16 50 mg/m^2 on days 1−10. The combination was well-tolerated and demonstrated antitumor activity, preserving the quality of life.

4104 ORAL

Does childhood cancer affect the parents' divorce rate? A population-based study

A. Syse[1], J.H. Loge[2], T.H. Lyngstad[3]. [1]*Cancer Registry of Norway, Dep. 1, Oslo, Norway;* [2]*Oslo University Hospital/Norwegian Radium Hospital, Dep. Long-term effects of cancer, Oslo, Norway;* [3]*University of Oslo, Department of Sociology, Oslo, Norway*

Background: Cancer in children may have a profound impact on couples' personal relationships both in terms of psychological stress, but also due to an increased parental care burden associated with chronic illness in a child. This could be hypothesized to elevate divorce rates among these couples, but few studies on divorce occurrence exist. The effect of a child's cancer on parental divorce rates was therefore explored.

Materials and Methods: Data on the entire Norwegian married population aged 17−69 with children under the age of 20 in 1974–2001 (N = 1.04 million couples) was retrieved from the Cancer Registry, the Central Population Register, the Directorate of Taxes, and population censuses. Divorce rates for 4524 couples with a child with cancer were compared to those of otherwise similar couples by means of discrete-time hazard regression models.
Results: Cancer in a child was not associated with an increased risk of parental divorce overall, or for any of the more common cancer forms among children. A tendency towards an increased divorce risk (OR 1.34, CI 1.00−1.81) was observed for parents' of children with renal cancers (primarily Wilm's tumor). Neither age, time from diagnosis, nor prognosis influenced the estimates adversely. The death of a child with cancer did not influence the divorce rates significantly in either direction. Couples with mothers with an education above high school level did, however, display significantly increased divorce rates (OR 1.19, CI 1.05−1.36). The risk was particularly high shortly after diagnosis. Other risk factors for these couples were CNS cancer, age 5−9 years, and death of a child.
Conclusions: This large registry-based study has shown that contrary to existing myths, cancer in a child is not associated with an increase in parental divorce risk. An exception exists for couples with highly educated mothers. This may relate to these mothers' wish to work outside the home, which may be difficult given an increased care burden at home. Shared parental responsibility for children and thus a shared provision of care is more common among women with a high education versus a low education in Norway. Further studies are, however, clearly warranted to understand the background for the observed increase in divorce risk for these couples.

4105 ORAL

Is institution a prognostic factor in adolescent and young adult patients with osteosarcoma?b

D. Carrle[1], B. Blank[1], M. Paulussen[2], P. Reichardt[3], S. Bielack[1]. *[1]Klinikum Stuttgart, Olgahospital – Pediatrics (Oncology Hematology Immunology), Stuttgart, Germany; [2]Universitätskinderspital beider Basel, Pediatric Oncology and Hematology, Basel, Switzerland; [3]HELIOS-Klinikum Bad Saarow, Sarkomzentrum Berlin-Brandenburg, Bad Saarow, Germany*

Background: Compared to paediatric cancer patients adolescents and young adults may have disadvantaged access to care. Therefore we investigated the correlation of patient, tumour and institutional characteristics with the outcome of osteosarcoma in this age group.
Material and Methods: Analysis of consecutive patients aged 15−24 years with newly diagnosed high-grade osteosarcoma entered into the Cooperative Osteosarcoma Study Group (COSS) registry 1980–2004 and treated in pediatric (PO) or medical oncology institutions (MO). Standardised multimodal therapy according to a COSS-protocol. Event-free survival rates (EFS) evaluated in relation to patient demographics and registering institution (MO vs PO and treatment volume as: $\leqslant$3 or >3 osteosarcoma/year).
Results: 944 patients identified (median age: 17.35 years; range: 15.01−24.99; 79% aged <20 years). Patients $\geqslant$20 years were more likely than younger patients to be treated in centers with low treatment volume ($p < 0.0001$) and MO ($p < 0.0001$) but otherwise comparable. After a median follow-up of 5.59 years (range: 0.12−27.92) for all patients and 8.08 years (range: 0.19−27.92) for 617 survivors, actuarial 5/10 year event-free survival probability (EFS) was 58%/54%. Upon univariate analysis of the total cohort neither of the institutional variables correlated significantly with EFS. There was a correlation between treatment in PO and improved EFS for patients $\geqslant$20 years ($p = 0.001$) and for those with primary metastases ($p = 0.009$). Upon multivariate testing type of center (odds ratio: 1.26; $p = 0.022$) but not treatment volume were significant.
Conclusions: Within a framework of standardised regimens and consultation support by our group's infrastructure, similar EFS-probabilites were obtained regardless of institutional treatment volumes. Observed variations in outcome between PO and MO may be partly due to different distributions of presenting factors but deserve further investigation.
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Poster presentations (Thu, 24 Sep, 09:00−12:00)
Paediatric oncology

4106 POSTER

Atypical Teratoid and Rhabdoid tumours in children: the French experience since 1998

A. Beaugrand[1], M. Quidot[2], P. Varlet[3], F. Bourdeaut[4], P. Leblond[5], J. Grill[1], M.C. Le Deley[2], C. Dufour[1]. *[1]Institut Gustave Roussy, Paediatrics, Villejuif, France; [2]Institut Gustave Roussy, Biostatistics, Villejuif, France; [3]Sainte-Anne Hospital, Neuropathology, Paris, France; [4]Institut Curie, Inserm U509 Laboratoire Pathologie Moléculaire des Cancers, Paris, France; [5]Centre Oscar Lambret, Paediatrics, Lille, France*

Background: To describe clinical features and therapeutic approaches and to identify prognostic factors in children with ATRT of the CNS.
Material and Methods: Observational study including all patients aged less than 18 years, diagnosed with CNS ATRT in France between January 1998 and July 2008, identified from hospital files and French Pediatric Cancer registry. Pathology review included histological and immunohistochemical analysis, including INI-1 staining. Impact of clinical characteristics (age, sex, site of primary tumor and metastatic status) on the overall survival (OS) was assessed using Cox models.
Results: seventy out of the 71 patients identified with ATRT over this 10-year period were included in the study (1 patient excluded due to incomplete clinical data). Median age was 2.8 years (range, 15 days – 12.8 years). Primary tumor site was supratentorial (ST) in 34, posterior fossa (PF) in 30, mixed (ST+PF) in 2 and medullar in 4 patients. The disease was disseminated at diagnosis in 22 patients. Five patients had non-CNS disease associated with CNS disease. Surgical resection was complete in 41 patients. Adjuvant therapy included chemotherapy in 55 cases and radiotherapy in 20 patients. Chemotherapy regimens were not standardized more than the study period: ATRT04, PNET High Risk and BB SFOP protocols were most frequently used. Median follow-up was 52 months (range, 13 months – 10 years). Disease progression or relapse occurred in 51 children. Median time to progression/relapse was 4.4 months. Median survival time was 9.9 months. One-year progression-free survival and OS were 21% and 42%, respectively. Metastatic status at diagnosis was the only prognostic factor (Hazard ratio for death: 2.1, 95%CI: 1.2−3.8, $p = 0.01$).
Conclusion: Children with ATRT of the CNS have a dismal prognosis. Innovative therapeutic are urgently needed.

4107 POSTER

Extended low-dose temozolomide induces severe lymphopenia in children with brain tumours: a phase II clinical trial

V. Ridola[1], G. Barone[1], I. Lazzareschi[1], A. Ruggiero[1], D. Rizzo[1], R. Riccardi[1]. *[1]"A. Gemelli" Hospital UCSC, Department of Pediatric Oncology, Roma, Italy*

Background: Standard schedule temozolomide (TMZ) with oral daily doses 200 mg/m^2 for 5 days every 4 weeks, has been utilized in children with progressive or relapsed brain tumours or with high grade glioma (HGG) at diagnosis. With this schedule manageable hematological toxicity and limited antitumor activity have been observed. Clinical and preclinical studies have shown that TMZ activity is highly schedule dependent. Extended TMZ dosing regimens may be more effective that standard regimens resulting in an higher cumulative dose over time.
Patients and Methods: We assessed the toxicity of a new extended low-dose schedule of TMZ in children with progressive or relapsed brain tumours or with HGG at diagnosis. Seventeen children were considered eligible for the study. Median age at diagnosis was 12.5 years (1 y-17 y). A total of 156 courses were administered, with a median number of 6 courses per patient (range: 2−22). TMZ was administered at 70 mg/m^2/day orally for 21 days every 28 days, as reported in adults studies. Heavily pre-treated patients started at a dose of 50 mg/m^2/day. Histological diagnosis showed 5 Ependymomas, 3 Low Grade Gliomas, 9 High Grade Gliomas.
Results: No toxic deaths or extra-haematological toxicity occurred. Grade IV and III lymphopenia occurred in 22.4% and 10.8% of courses, respectively. Grade III thrombocytopenia occurred in 0.6% of courses. Grade IV and III neutropenia occurred in 1.9% and 0.6% of courses, respectively. Among the patients showing lymphopenia, we observed 1 case of disseminated Zoster (meningoencephalitis and cutaneous involvement), 1 case of prolonged Rotavirus gastroenteritis, and 2 cases of herpetic stomatitis. The objective response rate was 11.8%. Overall, 82.3% of patients showed stable disease.
Conclusion: Our extended schedule was safe and well tolerated. No further cases of neutropenia or thrombocytopenia were observed despite the higher cumulative dose of the drug. Nevertheless, the prolonged