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

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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.

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

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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.

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

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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.

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

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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.