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Treatment of new cases of acute promyelocytic leukaemia by arsenic trioxide

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Purpose: Arsenic Trioxide approved for treatment of relapsed or refractory APL to ATRA. We studied the effects of Arsenic Trioxide as first line treatment of new cases of APL and their follow up.
Material and Methods: we studied 63 new cases of APL diagnosed by morphologic criteria and confirmed by cytogenetic, RT-PCR for PML/RARA and/or FISH.
Our patients were 28 males and35 females with median age 27±11.98. Patients treated by infusion of 0.15mg/kg/d of Arsenic Trioxide to complete remission by morphologic criteria or till day +60. In patients who complete remission achieved, after 28 days rest, again we began Arsenic Trioxide 0.15mg/kg/d for 28 days as consolidation.
Results: complete remission were achieved in 57 patients(90.5%) and 6 early mortality. Median time to complete remission was 30+/-6.6 days. Most common cause of mortality was APL maturation syndrome (4 cases)
Most common toxicities during induction phase were, APL maturation syndrome (14.7%), serositis(11.4%) and hepatotoxicity (18%).
88.5% of patients are alive with a mediam follow up of 12+/-10.02 months. 11 relapses observed in our patients and complete remission achieved with retreatment by Arsenic trioxide in 8 of them.
Mean survival time of patients by Kaplan-Meier method was 33.91 months (CI95% 30.98–37). Most common cause of death were APL maturation syndrome in 3 patients and relapse in 3 cases.
Conclusion: Arsenic Trioxide is acceptable as first line treatment of APL and its result is comparable to ATRA with chemotherapy.

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Nuclear survivin is a powerful novel prognostic marker in gastroenteropancreatic neuroendocrine tumour disease

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Background: Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) represent a rare and rather heterogeneous tumour entity. The growth pattern of GEP-NETs ranges from very slowly to fast growing, aggressive types of tumours. Survivin, a member of the family of apoptosis inhibitors, is a bifunctional protein that suppresses apoptosis and regulates cell division.
Aims: Here we determined the prognostic value of survivin in a series of GEP-NETs.
Patients and Methods: Tumour specimens from 104 patients (38 foregut, 53 midgut, 13 hindgut NETs) were studied immunohistochemically for cytoplasmic and nuclear survivin expression as well as for ki-67 antigen expression. 5-year-follow-up was complete in 89 patients. 29 patients with non-metastatic, well-differentiated GEP-NETs had been curatively treated by surgical or endoscopic tumour resection; therefore they were excluded from statistical analysis of survival. Kaplan-Meier-survival curves were calculated for 60 patients with advanced metastatic GEP-NETs.
Results: No recurrencies or tumour-associated deaths occurred in the 29 patients with localised well-differentiated GEP-NETs. All tumours of this group were negative for nuclear survivin. In the 60 patients with advanced metastatic GEP-NETs 15/60 (25%) tumours were nuclear survivin positive. Those 15 patients had a statistically significant worse prognosis (survival of 8 versus 115 months, $p<0.00001$). Nuclear survivin expression was strongly correlated with the differentiation grade of the tumour: Only 3/47 well-differentiated tumours displayed nuclear survivin, but 12/13 undifferentiated tumours did so.
Conclusions: Nuclear survivin expression appears to be upregulated during progression of GEP-NETs. The analysis of nuclear survivin expression identifies subgroups in metastatic GEP-NETs with good (survivin-) or with less favorable prognosis (survivin+). We propose that the determination of nuclear survivin expression could be used to individualize therapeutic strategies in GEP-NETs in the future.

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A phase I and pharmacokinetic (PK) study of an agonistic, fully human monoclonal antibody, HGS-ETR2, to the TNF-alpha related apoptosis inducing ligand receptor 2 (TRAIL R2) in patients with advanced cancer

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Introduction: A primary goal of cancer therapy is the selective induction of apoptosis in tumour cells. TRAIL induces apoptosis in a wide variety of cancer cells, whilst sparing most normal cells, by activating its death receptors TRAIL R1 (DR4) and TRAIL R2 (DR5) and downstream caspases. HGS-ETR2 is a high-affinity, recombinant fully human, $IgG_{1\lambda}$ monoclonal antibody (mAb) agonistic and specific to TRAIL R2. It induces apoptosis in TRAIL R2-expressing human tumour cell lines and tumour regression in established xenografts.
Methods: HGS-ETR2 was administered by IV infusion every 3 weeks at 0.1, 0.3 (4 pts each; 30 minute infusion) and 1 mg/Kg (6 pts; 2 hour infusion).
Results: Fourteen patients (age range: 25–70 years; 11 males) have received a total of 34 doses (range: 1 to 8 doses per patient) of HGS-ETR2. A patient with rapidly progressing metastatic chondrosarcoma has had continuing disease stabilization, receiving 8 courses of HGS-ETR2 to date. HGS-ETR2 has been well tolerated with minimal toxicity. One patient who received 1 mg/Kg developed CTCAE grade 3 asymptomatic rise in his serum amylase, detected on day 15 of course 1, resolving to grade 2 on day 23 and to baseline by day 43. This may have been related to the concurrent administration of ciprofloxacin. A further five patients were treated at this dose level without dose limiting toxicity or serious adverse events. Preliminary pharmacokinetic results are consistent with a two-compartment model with first-order elimination from the central compartment. At 0.3 mg/kg, the $t_{1/2\beta}$ranged from 10.03 to 14.98 days with a clearance that ranged from 4.28 to 4.83 mL/day/kg. The volume of distribution at steady state ranged from 65 to 88 mL/Kg and is 1.6 fold larger than the volume of distribution of the central compartment, indicating that HGS-ETR2 distributes to tissues. No HAHA antibodies have been detected thus far.
Conclusion: HGS-ETR2 administration is well tolerated and further dose escalation is anticipated.

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BARD1 required for telomere maintenance and control of genomic stability

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BARD1, the major protein binding partner of BRCA1, acts together with BRCA1 in repair functions upon genotoxic stress and ubiquitination. Mutations in BARD1 or BRCA1 predispose to cancer of the breast and ovary. A BRCA1-independent function of BARD1 was discovered in signalling from genotoxic stress to apoptosis. Upregulation of BARD1 in vivo, as observed upon stress, or overexpression in vitro lead to stabilization of p53 and induction of apoptosis. Repression of BARD1, by stable expression of BARD1 antisense RNA, results in genetic instability and resistance to apoptosis inducing drugs (Irminger-Finger et al., JCB 1998; Mol Cell 2001). Since BARD1 is upregulated upon genotoxic stress in vitro and in vivo, and triggers apoptosis by binding and stabilizing p53, it acts as critical messenger between genotoxic stress and apoptosis.
Mice deficient for telomerase show increased levels of apoptosis in a number of tissues but also increased incidence of tumorigenesis associated with genomic instability due to telomere attrition. We hypothesized that BARD1 might be involved in signalling from critically short telomeres towards apoptosis, since BARD1 repression or deficiency causes a premalignant phenotype (Irminger-Finger et al., 1998) and genomic instability (Irminger-Finger et al., 1998; Joukov et al., 2001; McCarthy et al., MCB, 2003).
To investigate this issue, telomere length was measured in BARD1-repressed or deficient cells by FISH and flow-FISH. We demonstrate that BARD1 repression is associated with a high degree of genetic instability and aneuploidy, and chromosomal aberrations, due to telomeric fusions. We further show that cell lines with stable repression of BARD1, TAC-2/ABI (Irminger-Finger et al., JCB 1998), and ovarian cancer cells missing functional BARD1, NuTu-19, have short telomeres, genomic instability, and