Patient reported abdominal pain as a surrogate of the clinical benefit of tipifarnib in pancreatic cancer patients

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BACKGROUND

The CXCL12/CXCR4 pathway mediates tumor cell homing and tolerogenesis of the immune system. Tipifarnib is a farnesyl transferase inhibitor currently in development in a registration-directed study in HRAS mutant head and neck cancer. Several lines of evidence indicate that tipifarnib is a CXCL12/CXCR4 pathway inhibitor:

- Proof of concept was achieved in a phase 2 cohort of patients (pts) with angiomyoblastic T cell lymphoma (AITL), a tumor that overexpresses CXCL12. CXCL12 expression was associated with response. Two complete responses (CR), 3 PRs and 4 disease stabilizations (90% clinical benefit) were observed in 10 pts with relapsed/refractory AITL and other peripheral T cell lymphomas overexpressing CXCL12 in lymphoid tissues, while 1 PR and no disease stabilizations were observed in 14 pts with low CXCL12 expression (p=0.05)
- Seven CRs were observed in 11 elderly/unfit acute myeloid leukemia (AML) pts expressing high levels of CXCL12 in bone marrow (Study CT020, pts with NRAS wt or unknown) while 1 CRs was observed in 16 pts with low bone marrow CXCL12 expression (p=0.03)
- Ex vivo transduction of bone marrow stromal cell cultures with tipifarnib decreased secretion of CXCL12

Based on these preliminary results, we have investigated other clinical settings in which activity of the CXCL12/CXCR4 pathway from tipifarnib treatment CXCL12 is a known poor prognosis factor in pancreatic cancer.

METHODS

- PATIENTS: Study INT-11 was a randomized, double-blind, placebo-controlled trial of gemcitabine + tipifarnib versus gemcitabine + placebo in patients with advanced pancreatic adenocarcinoma previously untreated with systemic therapy. Tipifarnib was given at 200 mg bid orally continuously; gemcitabine was given at 1,000 mg/m² intravenously weekly x 7 for 8 weeks, then every 3 every 4 weeks. A total of 688 patients were enrolled. The median overall survival for the experimental arm was 6.4 vs 6.1 months for the control arm (P = .75). Neutropenia and thrombocytopenia grade 3 or 4 were observed in 40% and 15% in the experimental arm patients versus 30% and 12% in the control arm. Clinical trial information: NCT00061648

- METHODS: Tumor gene expression from databases in TCGA and GEO databases was investigated. The Kaplan Meier method was employed to obtain survival probabilities. Spearman rank order correlation coefficients were determined to measure the strength of association between variables.

RESULTS

CXCL12 AND IGF1 ARE CO-EXPRESSED IN MANY TUMORS

- Analysis of gene expression in 24 tumor datasets from TCGA, Provisional, with over 8,000 PRs sampled, indicated that CXCL12 and IGF1 are highly co-expressed, suggesting a conserved functional interaction between these genes.
- Notably, the highest CXCL12/IGF1 co-expression was observed in indications in which responses to tipifarnib as monotherapy have been previously reported such as breast cancer, bladder cancer or acute myeloid leukaemia1,2

DISEASE MODEL FOR CXCL12 MEDICATE TUMOR HOMING TO LIVER AND LYMPH NODES

- Tipifarnib downregulates CXCL12 and may provide clinical benefit to subsets of pancreatic cancer pts.
- Patients with disease limited to lymph nodes or liver metastases, and those with no abdominal pain appear more likely to benefit from tipifarnib.
- Low KRAS mutant allele frequency (< 5%, ~30% pancreatic cancer pts) could help identify subjects with tumors overexpressing CXCL12.

The effects of a crosstalk between the IGFL and CXCL12 pathways are being further investigated.

CONCLUSIONS

- Tipifarnib downregulates CXCL12 and may provide clinical benefit to subsets of pancreatic cancer pts.
- Patients with disease limited to lymph nodes or liver metastases, and those with no abdominal pain appear more likely to benefit from tipifarnib.
- Low KRAS mutant allele frequency (< 5%, ~30% pancreatic cancer pts) could help identify subjects with tumors overexpressing CXCL12.

REFERENCES: 