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Results of PX-171−003-A0, part 1 of an open-label, single-arm, phase 2 study of carfilzomib in patients with relapsed and refractory multiple myeloma

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Background: Carfilzomib (CFZ) is a novel proteasome inhibitor of the epoxyketone class that exhibits a high level of proteasome selectivity and demonstrates antitumor activity in bortezomib (BTZ)-resistant multiple myeloma (MM) patients (pts) in phase 1 studies.
Methods: PX-171−003-A0 was an open-label, multicenter study that enrolled MM pts who relapsed from >2 prior therapies, failed BTZ and at least 1 immunomodulatory agent [thalidomide (THAL) or lenalidomide (LEN)], and were refractory to last treatment [progressing on or within 60 d of last therapy or <25% response to last therapy]. Pts received CFZ 20 mg/m^2 IV d 1, 2, 8, 9, 15 and 16 every 28 d for up to 12 cycles (C). Clinical benefit response (CBR) was defined as MR or better.
Results: 46 pts were enrolled, including 78% with progression on or within 60 d of last therapy and 22% with no response to last therapy. 39 pts completed at least 1 C of CFZ, had measurable M-protein, and were evaluable for response. Median prior therapies was 5 (range 2−15). 100% of pts received prior BTZ, 91% prior THAL, 89% prior LEN, and 83% prior stem cell transplant (SCT) and all had failed combinations including anthracyclines (80%) and/or alkylating agents (94%). Pts received a median of 3 C (range 1−12); 13 pts completed ⩾6 C. CBR was 26% (10/39 eval pts), including 5 pts achieving PR and 5 pts achieving MR. 5 BTZ-refractory pts achieved MR or PR. Median TTP was 6.2 mo, the median DOR for the MR + PR was 7.4 mo. 8/10 pts achieved response during C1. 16 additional pts achieved SD for at least 6 wks. The most common adverse events were fatigue, anemia, thrombocytopenia, nausea, upper respiratory infection, increased creatinine and diarrhea. Peripheral neuropathy occurred in <10% of pts with 1 Gr 3 in a pt with pre-existing Gr 2. The FACT/GOG-NTX QOL was improved over baseline.
Conclusions: Single-agent CFZ achieved a TTP of > 6 mo in relapsed and refractory MM pts who failed available therapies. 26% of patients had at least an MR and median duration of >7 mo with this steroid- and anthracycline-sparing regimen. CFZ toxicities were manageable and importantly, exacerbation of pre-existing PN was rare. The study has been expanded to enroll an additional 250 pts in this unmet medical need population at an stepped-up dose schedule of 20/27 mg/m^2.

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Array based CpG island methylation-profiling in acute myelogenous leukemia at diagnosis and relapse

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Background: In acute myelogenous leukemia (AML), pathological hematopoietic progenitor or stem cells show uncontrolled proliferation and arrest in maturation. Cytogenetic analyses have identified specific recurrent chromosomal aberrations. Additionally, methylation of cytosines in the promoter region of many genes is involved in regulating gene expression. In this study we used the Illumina GoldenGate© methylation assay to assess the methylation status of a large number of selected genes in 32 AML patients at diagnosis and relapse, compared to normal controls.
Material and Methods: We obtained 31 bone marrow (BM) and one peripheral blood specimen during routine clinical assessment of 32 patients with newly diagnosed AML treated at the University Hospital Aachen (Germany) from 1997 to 2008 and used 11 non-malignant BM specimens and four peripheral stem cell harvests as controls. From nine of the 32 AML patients, BM at time of relapse was also available. The methylation status of 1505 CpG-sites from 807 genes was simultaneously determined using the GoldenGate© Methylation Cancer Panel I assay (Illumina, San Diego, CA, USA), which provides a continuous measure of methylation density ("β-value" between 0.0 and 1.0) of each site. For comparison, methylation-specific PCR (MSP) was performed for two genes (SFRP1 and CDKN2B).
Results: Cluster analysis of array results revealed a similar methylation profile among the normal controls compared to AML samples at diagnosis. Within the AML samples, an association between methylation patterns and recurrent cytogenetic aberrations such as del(5), del (7), inv (16) and t (8;21) could also be found. Overall, methylation in AML samples was higher than in the controls (mean β-value 0.3449 vs. 0.3084). We identified 216 CpG-sites that were mostly unmethylated in controls but yielded significantly higher methylation in the AML samples. For 12 sites, a significant correlation between methylation status and survival could be detected. Comparing the nine corresponding samples at diagnosis and relapse, only small changes in the methylation profile and a slight increase in overall methylation (0.3491 vs. 0.3361) were detected at time of relapse. Additionally, we found a strong correlation between the results of array analysis and MSP.
Conclusions: Hypermethylation is a frequent event in AML and is accentuated at relapse. Array-based methylation analysis of a large number of genes determined distinct methylation profiles for normal controls and AML samples with specific chromosomal aberrations. The methylation status of several specific genes had a significant impact on survival.

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Lipoxin A4 accelerates the resolution of acute promyelocytic leukemic cells in retinoic acid syndrome

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Background: Retinoic acid syndrome (RA syndrome) may develop in patients with acute promyelocytic leukemia (APL) during treatment with all trans retinoic acid (ATRA), which is characterized by which is characterized by massive infiltration of ATRA-treated APL cells into alveolar spaces. Resolution phase of RA syndrome has not been studied. Lipoxin A4 is an anti-inflammatory mediator during acute inflammation and its role in RA syndrome is still unknown.
Materials and Methods: We determined the crosstalk between the ATRA-treated APL (NB4) cells and alveolar macrophages (NR8383 cells) by transmigration assay, phagocytosis assay and ELISA.
Results: Condition medium (CM) of co-culture of alive NR8383 cells and dead ATRA-treated NB4 cells can inhibit the transmigration of alive ATRA-treated NB4 cells in a dead NB4 cells dose-dependent manner. The level of lipoxin A4 in the CM increased when a fixed number of alive NR8383 cells were co-cultured with increased cell number of dead ATRA-treated NB4 cells. Lipoxin A4 itself can inhibit the transmigration of ATRA-treated NB4 cells in a dose dependent manner. Receptor of lipoxin A4 (FPRL-1) was expressed in both ATRA-treated NB4 cells and NR8383 cell by immunohistochemical stain and flowcytometry. BOC-2 (inhibitor of FPRL-1) can further increase the transmigration of ATRA-treated NB4 cells, indicating the active role of lipoxin A4 in the ATRA-treated NB4 cells. We also demonstrated that lipoxin A4 can enhance the phagocytosis of dead ATRA-treated NB4 cells by NR8383 cells.
Conclusion: Lipoxin A4 can inhibit the transmigration of ATRA-treated APL cells and increase the phagocytic activity of alveolar macrophages. This indicates that lipoxin A4 contributes an important role in the resolution phase of RA syndrome.

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Polymorphisms of genes MDR1 and MTHRF in children with acute leukemia

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Background: The objective of this study is to evaluate the polymorphism frequency of MDR1 (multidrug resistance) and MTHRF (5,10-methylenetetrahydrofolate reductase) genes which can modulate the risk of acute leukemia.
Material and Methods: The study included 30 patients with acute myeloid leukemia (AML), 40 patients with acute lymphoblastic leukemia (ALL) and control group composed of 31 individuals without leukemia. The age of children ranged from 0 to 22 years (median 7 years). Gender distribution