

Abstract

Title I: Aurora kinase and FGFR3 inhibition results in significant apoptosis in molecular subgroups of multiple myeloma

In our pre-clinical study we examined the role of Aurora kinase and FGFR3 inhibition in MM using a small molecule inhibitor A1014907 which induced aneuploidy in MM cell lines at low nanomolar doses. However, A1014907 induced more pronounced and dose dependent apoptosis in cell lines with t(4;14) translocation. Translocation t(4;14) is observed in about 15% of patients with MM leading to constitutive activation of FGFR3 in two-thirds of these patients. Further investigation of the mechanism of action of A1014907 revealed potent FGFR3 pathway inhibition only in the sensitive cell lines. Thus, our results show that aurora kinase inhibition causes cell cycle arrest and aneuploidy with minimal apoptosis whereas inhibiting both aurora kinase and FGFR3 activity induced potent apoptosis in MM cells. This study evaluates the role of simultaneous inhibition of Aurora Kinases and FGFR3 pathway which are both important deregulated pathways in MM patients; inducing potent apoptosis.

Title II: Natural history of multiple myeloma with de novo del(17p)

Our clinical study involved comparing the outcomes of 310 newly diagnosed MM patients with del(17p) detected by FISH to patients with high-risk translocations (HRT) ($n = 79$) and standard-risk (SR) cytogenetics ($n = 541$). The median progression-free survival (PFS) following initial therapy for the three groups was 21.1, 22, and 30.1 months, respectively ($P = 0.437$ - del(17p) vs. HRT); the median overall survival (OS) was 47.3, 79.1, and 109.8 months, respectively, ($P = 0.007$ - del(17p) vs. HRT). PFS and OS for patients with relative loss of 17p ($n = 21$) were comparable to other patients with del(17p). The PFS was similar between the del(17p) and HRT groups when stratified for age, ISS stage or treatment. The OS of del(17p) and HRT groups were similar in presence of advanced age, ISS III stage or if patients did not receive a proteasome-inhibitor containing induction. ISS III stage, high LDH and HRT, but not the percentage of cells with del(17p) predicted shorter OS in patients with del(17p).

This study identified, factors predictive of OS in patients with de-novo MM and also found no difference in outcomes for patients with relative loss of del17p.

Title III: Impact of acquired del(17p) in multiple myeloma

We next studied the impact of acquiring del17p after the diagnosis of MM as the role of late acquisition of this deletion is not well described. The disease characteristics at diagnosis predicting for acquired del(17p) and its overall impact on patient survival is also not well studied.

We compared 76 patients with MM who were del(17p) negative at diagnosis, and acquired it later, and compared them to 152 control MM patients who did not acquire del(17p) at a comparable timepoint. Patients acquired del(17p) at a median of 35.6 months (range, 4.6-116.1) from diagnosis of MM, after a median of 2 (range, 1-10) lines of treatment. Patients with acquired del(17p) when compared to controls, had shorter median progression free survival (PFS) [23.0 vs. 30.1 months; P=0.032] and overall survival (OS) [68.2 vs. 106.1 months; P<0.001] from diagnosis.

The median PFS and OS after the detection of del(17p) were 5.4 months and 18.1 months respectively. High lactate dehydrogenase level [OR-3.69 (95% CI, 1.11-12.24)], and presence of t(4;14) [OR-2.66 (95% CI, 1.09-6.48)] or any high risk translocation [OR-2.23 (95% CI, 1.00-4.95)] at diagnosis predicted for acquisition of del(17p). High PC proliferative rate predicted shorter OS from detection of del(17p) [hazard ratio - 2.28 (95% CI, 1.31-3.96) (P=0.004)].

Our study shows that acquisition of del(17p) is an important molecular event associated with reduction in OS in MM. Certain baseline factors may predict acquisition of del(17p). This needs validation in prospective datasets.