Aim: Ewing sarcoma (ES) is an aggressive form of primary bone cancer affecting mainly children and young adults. Despite intensive multimodal treatment, survival has not improved much during the last decade and therapeutic options in second line are scarce. Therefore, the search for novel, targeted therapeutic strategies has a high priority. Here, we investigated for the first time the expression and genetic aberrations of AXL, an oncogenic receptor tyrosine kinase (RTK), in ES and determined the efficacy of AXL-targeting on cell viability and migration in vitro.

Methods: AXL and Gas6 (ligand) mRNA expression were determined by RT-PCR on 29 fresh-frozen ES patient samples. AXL protein expression was determined immunohistochemically in 36 tumors (primary tumors, post-chemotherapy resections, metastases and relapses) from 25 ES patients. Kaplan-Meier analysis (log-rank test) was performed to draw and evaluate the significance of survival curves. The AXL RTK domain and Gas6 were sequenced in 29 ES tumors. Six ES cell lines (ES1, ES2, ES4, ES7, ES8 and EW8) were treated in vitro with the specific AXL-inhibitor BGB324 (R428) and viability was analyzed with MTT-assays. In vitro migration assays were performed to investigate effects of BGB324 on ES cell migration.

Results: Low, medium and high AXL mRNA expression was observed in 31% (n=9), 48% (n=14) and 21% (n=6) of ES samples, respectively. Gas6 was abundantly present in all specimens. Low, medium and high AXL protein expression was observed in 16% (n=6), 18% (n=7) and 34% (n=13) of ES samples. In primary tumors (n=15), high AXL expression correlated significantly with a worse overall survival (OS) compared to patients with lower expression (61 vs. 194 months, p=0.026). No genetic aberrations were observed in the AXL RTK domain or Gas6. BGB324 dose-dependently affected ES cell viability (IC50 0.79 - 2.13 μmol/L) and migratory potential (~2 times delayed wound closure) in vitro.

Conclusions: Our data suggest that AXL is a potential novel therapeutic target in ES. We are currently examining the effects of BGB324 on human derived ES xenografts in vivo. Because AXL-targeting drugs, such as BGB324, entered the phase of clinical trials, AXL targeting may potentially be of interest for further exploration in the clinical ES setting.

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