SKIN CANCER (OTHER THAN MELANOMA)

THE PI3K/MTOR DUAL INHIBITOR PF-04691502 HAS ANTITUMOR ACTIVITY IN CUTANEOUS T-CELL LYMPHOMAS

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Introduction: Cutaneous T-cell Lymphomas (CTCLs) are a subset of non-Hodgkin's lymphoma, localized to the skin. Mycosis Fungoides (MF) is the most diffuse form (almost 50%), a slow-growing type, treatable, but not curable. 5% of CTCLs are Sezary Syndrome (SS), an aggressive variant with erythroderma, leukemia, and lymph node involvement. Poor prognosis of SS and advanced MF needs the development of new therapies. Genomic data previously obtained in our laboratory showed that the tumor-suppressor PTEN was deleted in 39% of 44 SS patients. Recently, we described the hyper-activation of PI3K/AKT/mTOR pathway in SS patients. Hence, inhibitors of the PI3K/AKT/mTOR pathway represent potential therapeutic compounds against CTCL.

Objective: The aim of this study was to investigate the therapeutic potential of the pan-PI3K/dual-TORC1/2 inhibitor PF-04691502 (hereafter PF-502) against CTCL.

Materials and Methods: PF-502 antitumor activity was evaluated in 2 SS and 2 MF cell lines and in patient-derived SS cells, for its ability to inhibit cell growth (MTT assay), to induce apoptosis and cell cycle block (flow cytometry) and to inhibit chemotaxis toward the chemokine SDF-1 (migration test). Moreover, PF-502 efficacy was evaluated in a xenograft mouse model.

Results: We observed cell growth inhibition upon PF-502 treatment in the 4 CTCL cell lines (IC50 ranging from 0.07 to 0.32 µM), and in 5 SS patients (mean IC50 at 2.3 µM). PF-502 effect in CTCL cell lines is due to a combination of apoptosis and G1 block, while in SS patients it is due to huge apoptosis induction. In addition, PF-502 inhibits cell migration toward SDF-1 in both CTCL cell lines and primary SS cells. Importantly, PF-502 only partially affected viability of T-lymphocytes from 3 healthy donors. Finally, PF-502 reduced tumor growth and prolonged survival in the xenograft mouse model.

Conclusions: Our data strongly support the therapeutic potential of PI3K/mTOR dual inhibitors against CTCL.