

Pancreatic Cancer

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Anti-Cancer Effect and Mechanism of Combination of Suberoylanilide Hydroxamic Acid (SAHA) and Bortezomib with Gemcitabine in Pancreatic Cancer Cell Lines

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Background: Pancreatic cancer is one of the most formidable gastrointestinal cancers because most patients are unresectable at the time of diagnosis. Gemcitabine is the standard treatment for advanced pancreatic cancer, although response rate is low and life expectancy is poor, underscoring the need for more effective therapy. In recent years, combinations of novel anti-cancer drugs including histone deacetylase (HDAC) inhibitors and proteasome inhibitors have been tried for various cancers; however, few data are available on these agents in pancreatic cancer. This study was conducted to assess the effects of such agents with or without gemcitabine in pancreatic cancer cell lines and to explore possible mechanisms.

Methods: The effects of suberoylanilide hydroxamic acid (SAHA), a novel HDAC inhibitor, and bortezomib, a selective inhibitor of 26S proteasome, with or without gemcitabine, on cell growth and apoptosis and the expression of related proteins were observed in pancreatic cancer cell lines (MiaPaCa-2 and ASPC-1). The xenograft model of pancreatic cancer was employed to study effects in vivo.

Results: SAHA and bortezomib demonstrated anti-tumor properties in pancreatic cancer, and more enhanced effects were noted when these agents were combined with gemcitabine than when gemcitabine was used alone in vitro. In the xenograft model, effects were augmented when SAHA was combined with gemcitabine as compared with effects with gemcitabine alone. The triple combination of SAHA, bortezomib, and gemcitabine resulted in the strongest anti-tumor effects both in vitro and in vivo. Down-regulation of pAkt and Bcl-xL expression and suppression of NFκB activity were observed in the combination group.

Conclusion: The combination of SAHA and bortezomib enhanced the anti-tumor effect of gemcitabine in pancreatic cancer. Down regulation of pAkt and Bcl-xL expression and blockage of the NFκB pathway seemed to be involved in these processes.