YONDELIS® (trabectedin)
YONDELIS – Mechanism of Action

SUMMARY

- Trabectedin is an alkylating agent that binds the guanine residues in the minor groove of deoxyribonucleic acid (DNA), which leads to distortion of the double helix and bending toward the major groove, resulting in a cascade of events that interfere with several transcription factors, DNA binding proteins, and DNA repair pathways.[1-4]
- In preclinical studies, trabectedin caused transcriptionally-dependent cell cycle arrest during the S and G_2/M phases, leading to cell growth inhibition and, eventually, apoptosis.[5,6]

MECHANISM OF ACTION

Binding to Minor Groove of DNA

The chemical structure of trabectedin is comprised of 2 fused tetrahydroisoquinolone rings (Rings A and B) linked to a third tetrahydroisoquinolone ring (Ring C). Unlike traditional alkylating agents that bind to the DNA major groove, trabectedin binds the guanine residues in the minor groove of DNA, which leads to distortion of the double helix and bending toward the major groove.[1-3] Trabectedin preferentially binds DNA at the specific sequences of 5'-purine-guanine-cysteine and 5'-pyrimidine-guanine-guanine.[1] Ring C is not involved in the DNA binding and is thought to stick out of the DNA and interact with adjacent proteins.[1] These chemical interactions trigger a cascade of events directly involved in the oncogenic process that interferes with DNA binding proteins, transcription factors, and DNA repair proteins.[1,4]

DNA Repair

Binding of trabectedin to the minor groove appears to interfere with DNA repair pathways such as transcription-coupled nucleotide excision repair (TC-NER).[7] In vitro studies suggest that trabectedin protrudes from the minor groove and forms a complex with proteins of the TC-NER system, such as XPG, which inhibits the DNA repair mechanism and ultimately results in DNA double-strand breaks.[1,7] The activity of trabectedin also appears to involve homologous recombinant repair (HRR), another repair pathway that is involved in the repair of double-strand breaks. Cells with HRR deficiencies demonstrated increased sensitivity to trabectedin in vitro, and complementation of defects almost completely reverted sensitivity to normal control level.[8] These data suggest that HRR is a key determinant in repairing trabectedin-induced double-strand break lesions.

Transcription Regulation

At lower trabectedin concentrations in human cancer cells and in the yeast schizosaccharomyces, trabectedin causes transcriptionally-dependent cell cycle arrest during the S and G_2/M phases, leading to cell growth inhibition and, eventually, apoptosis.[5,6] At higher trabectedin concentrations in the yeast schizosaccharomyces, the cells stopped growing and died.[5] At higher trabectedin concentrations in human cancer cells, trabectedin causes transcription-independent cell cycle apoptosis by mitochondrial cytochrome c release, c-Jun NH_2-terminal kinase (JNK) activation, and caspase-3 activation.[6]

Effects on Tumor Microenvironment

In murine models, trabectedin induced selective depletion of monocytes/macrophages in blood, spleens, and tumors, along with a reduction of angiogenesis.[9] A reduction of monocytes, tumor-associated macrophages (TAM), and blood vessel density was also demonstrated in patients with soft tissue sarcoma who received trabectedin in the neoadjuvant setting. The selective effect of trabectedin on monocytes was shown to be mediated via caspase-8-dependent apoptosis. In other investigations, trabectedin inhibited

the production of proinflammatory mediators (CCL2 and IL-6) in stimulated monocytes, macrophages, and TAM of isolated ovarian tumor cells.[10] The inhibitory effect on cytokines was shown to occur at the transcriptional level. In human myxoid LPS cells, trabectedin decreased the number of inflammatory mediators, including CCL2, CXCL8, IL-6, VEGF, and PTX3 in vitro.[11]

Additional Data

The mechanism of action of trabectedin in myxoid/round cell LPS mouse xenograft models is theorized to involve displacement of the oncogenic protein FUS-CHOP from its promoters of target genes.[12] Functional inactivation of the FUS-CHOP chimera resulted in a displacement of an oncogenic transcription factor from its target DNA sequence in vivo, and consequent derepression of the adipocytic differentiation.

In vitro and in vivo studies demonstrated antitumor effects of trabectedin against clear cell sarcoma cells via G_2/M cell cycle arrest and apoptosis. In addition, trabectedin increased the expression of melanocytic differentiation markers by inactivating extracellular signal-regulated kinase (ERK) signaling.[13]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 19 April 2023.

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