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A review on trabectedin

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Abstract
Trabectedin is a drug which belongs to class Anti-Neoplastic agents and is available in a powdered dosage form for reconstitution. It is derived from *Ecteinascidia turbinata* which is a Caribbean marine tunicate. Trabectedin is also called as Ecteinascedin and is generally used for the treatment of Soft Tissue Sarcoma (STS) and in Ovarian Cancer. Unlike other neoplastic agents, Trabectedin binds to the minor groove of DNA which results in the structural changes of DNA that may cause cell death. Trabectedin also interferes with the transcription, repair pathway and also blocks G2 and M phase of cell cycle. Due to these events cell proliferation ceases. In this manner trabectedin shows its anti-tumor effects.

Keywords: trabectedin, anti-neoplastic agent, soft tissue sarcoma, ovarian cancer

Introduction

Trabectedin is a marine alkaloid that is isolated from the tunicate *Ecteinascidia turbinata*.

This is an anti-neoplastic drug which have been found efficient in the treatment of soft tissue cancers.

When it comes to the availability of the drug it's a bit of scarcity as it requires 1 ton of *Ecteinascidia turbinata* to produce 1 gram of Trabectedin which makes it a way more expensive.

To overcome this scientists have developed a semi synthetic method for the production of Trabectedin.

Amino acid Tyrosine is involved in the synthesis of trabectedin which forms an intermediate product which is used as a starting material for the production of two halves of trabectedin molecule which are binded together in the later reactions.

There are 2 to 3 Tetrahydroisoquinoline sub-units along with active carbinolamine functional group which are responsible for showing potent anti-proliferative activity.

The semi synthetic method of production of trabectedin involves readily available cyanosafracin B.

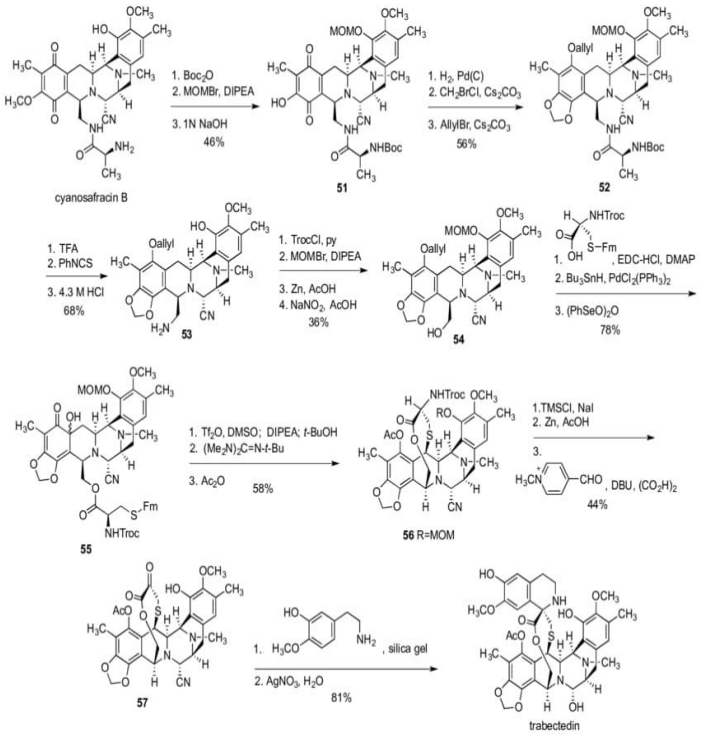

Fig 1

The above figure shows the steps involved in the production of trabectedin from cyanosafracin B.
Hence by synthesizing of Trabectedin synthetically the need of sea squirts for isolation of trabectedin have been decreased.

Mechanism
Although the exact mechanism is unknown till now, it have been noticed that trabectedin binds to the minor groove of DNA unlike other neoplastic agents which bind to major groove of DNA. After binding to the minor groove of DNA it bends the DNA towards the major groove and interferes with the Transcription Coupled Nucleotide Excision Repair pathway (TC-NER) which leads to structural changes in DNA that may cause its damage which alters its normal functions such as repair and transcription that ultimately leads to cessation of cell proliferation, cell differentiation and causes Apoptosis or Cell Death. It also blocks the G2 and M phase of cell cycle (selective inhibitor of transcription).

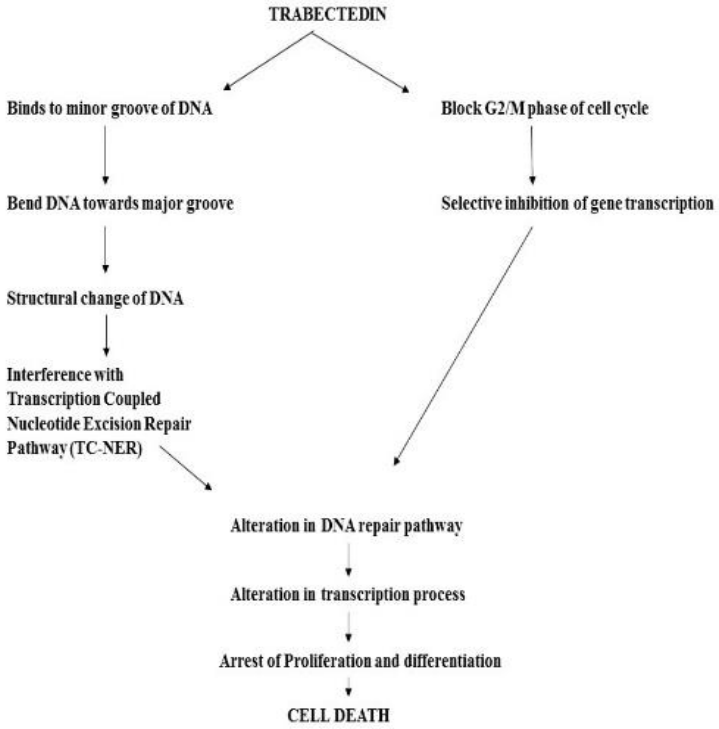

Fig 2

Pharmacological Properties
Distribution
Trabectedin is mostly administered intravenously and is extensively distributed in tissues.
Volume of distribution is greater than 5,000 L.
Protein bound- ~97%

Metabolism
Trabectedin is metabolized in liver by Cytochrome P450 (CYP) pathway.

Excretion
Extensively metabolized, with negligible unchanged drug in urine and feces.
Half-life of trabectedin is found to be 175hr.
Clearance – 31.5 L/hr.
Studies suggest that if Trabectedin is given in combination with other anti-neoplastic drugs it shows additive or synergistic effects.

Tolerability
Toxicity profile of trabectedin can be managed easily as it shows mostly grade I and grade II adverse effects and are reversible.
Grade III and grade IV adverse effects are severe. For example Neutropenia, in this neutrophil count is abnormally decreased.
The most frequent adverse effect was elevation of serum ALT or AST levels due to frequent treatment.

Trabectedin triggers NK-mediated Cytotoxicity in Multiple Myeloma
Multiple Myeloma is the cancer of plasma cells in which genomic instability is seen.
Alteration in DNA repair pathways contributes to the genomic instability.
Changes in Cytokine production and release was noticed.
Studies suggest that Trabectedin induces the activation of NK cells, DNA Damaging Response (DDR) and cellular stress with cell cycle arrest.
It was also found that trabectedin triggers apoptosis in multiple myeloma.
Drug-induced cell stress in multiple myeloma cells leads to upregulation of NK activating receptor ligands which results in increased NK cell activation and degranulation.

And hence it is found that trabectedin triggers NK-mediated cytotoxicity in multiple myeloma.

Trabectedin Decreases Skeletal Prostate Cancer Tumor Size

It decreases the tumor size and also shows effect on Macrophages and efferocytosis. Efferocytosis is a process in which the dead cells are removed by the phagocytic cells. Macrophages play a prominent role in regulating tumor progression as it can either reduce tumor growth or promote tumor growth.

Bone Marrow is rich with monocytic cells so it serves as the site for prostate cancer. Trabectedin is identified to have ability to induce apoptosis in macrophages and monocytes. Studies suggest that macrophage effects are important for trabectedin to exert its therapeutic benefits.

Studies suggests Macrophage efferocytosis as a critical cell function which increases prostate cancer cell growth. So far no curative treatment have been found for prostate cancer bone metastasis and most of the patients who die because of prostate cancer have involvement of bone.

Trabectedin is found to be able to target M2-like macrophages and their efferocytosis by which it shows its potential in treatment of prostate cancer skeletal metastatic tumor growth.

Antimetastatic and antiangiogenic activity of trabectedin in cutaneous melanoma

Cutaneous Melanoma is a serious skin cancer.

Apart from targeting cancer cells, Trabectedin also shows effect on tumor microenvironment, its vasculature and immune response.

Trabectedin shows significant reduction in the tumor blood vessel density and associated macrophages thereby inhibiting the subcutaneous growth of murine melanoma.

According to some studies, trabectedin also shows significant

Anti-metastatic activity thereby inhibiting the formation of lung colonies.

Trabectedin also inhibits melanoma cell invasiveness.

Hepatoprotective effect of N-acetyl cysteine in Trabectedin induced Liver Toxicity

Trabectedin is one of the most efficient anti-neoplastic agent used in the treatment of Soft Tissue Sarcomas but hepatotoxic effect is seen most frequently which represents a dose limiting factor.

N-acetyl cysteine is found to have antioxidant properties which shows hepatoprotective effect.

This makes us consider use of N-acetyl cysteine to overcome the major side effect that is liver toxicity which is induced by trabectedin.

Studies suggests that N-acetyl cysteine exert hepatoprotective activity in patients receiving trabectedin and to patients with impaired liver function and renal function.

Conclusion

Trabectedin is a drug that binds to guanine residues in the minor groove of DNA and causes bending of DNA towards major groove which triggers a cascade of events which affects the normal functioning of DNA and its activities such as DNA binding proteins, transcription, DNA repair pathways resulting in the perturbation of the cell cycle and eventual cell death.

In a simple way, Trabectedin is a minor groove binder that is able to induce DNA damage which alters the normal function of the DNA, its repair and transcription process leading to cessation of cell proliferation and cell differentiation and ultimately leads to cell death.

Trabectedin modulates the tumor microenvironment which can be a reason for its anti-tumor activity.

The hepatotoxicity induced by the trabectedin may lead to impaired liver function and this can be overcome by use of N-acetyl cysteine which is having anti-oxidant properties and exert hepato-protective effect thereby counteracting the important side effect which shows crucial clinical impact in drug induced hepatotoxicity.

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