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Review Article

Uridine triacetate: the saviour in waiting, finally arrives

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ABSTRACT

Cancer of the gastrointestinal tract is one of the very common solid cancers. Colorectal cancer is one of the types in which the anticancer drug 5-fluorouracil (5-FU) or its prodrug capecitabine is used. Toxicity to 5-FU or capecitabine is a common occurrence in patients receiving it. In such conditions, dose reduction or drug discontinuation for some time was the only way out apart from some supportive measures. An exhaustive search was always on to find a suitable antidote for the toxicity. The molecule uridine triacetate was studied for a long to be used in this condition. A systematic search of the existing literature about uridine triacetate was done with available sources like PubMed, Google Scholar, etc. Information about uridine triacetate was assembled and processed from these sources. Uridine triacetate was given orphan drug status for this indication a few years back. After a clinical trial, the drug was finally approved by the US FDA on December 11, 2015, for use in case of toxicity to 5- 5-FU or capecitabine. Well, stat Therapeutics has been marketing the drug under the trade name of Vistogard. Uridine triacetate works by preventing the toxic metabolite of 5-FU from entering and establishing itself in the RNA framework, by competing with the toxic metabolites. It is a relatively safe drug with minimal side effects. This article discusses the molecule uridine triacetate, its structure, metabolism, and kinetics in the body, the why and how of its action, and finally the results and findings of the clinical trial done with it.

Keywords: Toxicity, 5-FU, Capecitabine, Uridine triacetate

INTRODUCTION

The 5-fluorouracil (5-FU) is a pyrimidine analogue and a very potent drug used in the treatment of solid cancers of the gastrointestinal tract like colorectal cancers, cancer of the stomach, also in cases of breast cancers, and some head and neck cancers.[1,2] It also finds use as a topical drug in conditions like Bowen disease, actinic keratoses, and some types of basal cell cancers.[3,4]

The oral prodrug of 5-FU, capecitabine is even under investigation for potential use in the case of brainstem gliomas in pediatric patients.[5]

The 5-FU is an anticancer drug that shows synergy with many other anticancer drugs when given as a combination therapy with them. Also, it is of effect in tumors that have shown resistance to other modalities of cure.[6]

With deaths due to cancer being the most common cause across the world and being reported as the most common cause after cardiovascular events in the United States and with 5- FU claimed to be second in the list of most used drugs for cancer management about 10 years back it becomes imperative that we use this drug for maximum benefit of cancer patients and avoid or correct the reasons for discontinuation and dose reduction of the drug.[6-8]

As with most anticancer drugs 5-FU too, has its share of shortcomings, the most important being the development of toxicity, when the dose of the drug is increased for more efficient results or even sometimes if given in normal therapeutic doses or a dose considered to be close to

maximum dose allowed. This may happen due to various reasons like subnormal clearance of the drug from the body, and differences in metabolising enzymes at the genetic level. Apart from these, toxicity is bound to develop if the drug is administered too fast or more than the required dose due to some miscalculation.[9,10] Even the oral prodrug capecitabine which was developed to bypass some shortcomings seen with 5-FU is not free of toxicities.[9]

Somewhere close to 2,75,000 people undergo treatment with 5-FU in the United States every year for various indications. Out of these, we have close to 1300 mortalities due to these toxicities.[11]

TOXICITY REPORTS

When a woman of 43, suffering from nasopharyngeal cancer died in Canada because of accidental overexposure to fluorouracil, along with other anticancer drugs due to a dose calculation error by the attending nurse (she was infused with 5250 mg of 5-FU within 4 hours instead of 4 days). The patient developed symptoms like vomiting, and nausea and gradually over the ensuing days and weeks she developed pancytopenia, mucositis, and organ failure. Despite best efforts, the patient died on day 22 of exposure, in want of a suitable antidote for toxicity. Institute for safe medication practices (ISMP), Canada did a root cause analysis (RCA) of this event and concluded that the death was a consequence of toxicity caused by fluorouracil which could have been potentiated with cisplatin toxicity too, which was co-administered with it. They even found out a minimum of seven more such events in Northern America earlier.[12] They also concluded that these toxicities can occur if the dose given is 10% or more than the desired one or infused at a rate faster than 25% of the actual rate.[13]

As these reports of accidental overexposure have not been uncommon with 5-FU and its prodrug capecitabine, so following the FDA designation of uridine triacetate as an orphan drug for fluorouracil toxicity it was used in patients with overexposure to fluorouracil or capecitabine. An incidence of a 22-month-old male child suspected to have consumed a few 500 mg tablets of capecitabine was reported. The amount suspected to have been consumed by the child was considered a lethal dose. The child was admitted and treated with uridine triacetate. On reporting and during the treatment period, the child was active and the blood parameters were more or less normal, but after discharge on about the 12th day, a drop in absolute neutrophil count was observed which was considered mild given the amount of exposure to capecitabine he had. This prevention of a potential mishap was attributed to uridine triacetate as per the case reporters.[5]

One more case of a male patient of adenocarcinoma, aged 58 was reported, where he received 3400 mg of fluorouracil in a combination regime over 48 minutes instead of 48 hours, by mistake. Following this, he was administered filgastrim with uridine triacetate, though neutropenia and mucositis were observed on day 9, the patient recovered fully by day 14th. Another case of toxicity by capecitabine this time, was reported in a female 59 years suffering from carcinoma rectum. The woman mistakenly received 8000 mg of capecitabine in a single day instead of 2400 mg because she was delivered with 500 mg tablets of capecitabine instead of 150 mg. After 2 weeks the patient came with mucositis, diarrhea, and pancytopenia. The patient was provided intensive care for about a month following which she showed improvement.[14]

TOXICITIES-THE SCIENCE BEHIND IT

As 5-FU is an agent with a narrow therapeutic index of safety, its toxicities may even vary depending on the mode by which the drug reaches the body. The adverse reactions also cannot be predicted accurately in every individual as there are variations in their setting in because of inter-individual variation in the ability to metabolize 5-FU. In some people, there is a deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD), a very crucial enzyme in the metabolism of 5-FU. Administration of 5-FU in such patients can lead to catastrophic effects because of this genetic flaw.[10] In addition to these there can always be that chance of dose miscalculation leading to overdose or an overdose because of contraption flaw, even so much that a normal dose in less than stipulated period of time can lead to a mishap.[10]

While one might wonder that these kinds of misadventures can be prevented by being careful and meticulous, one has to understand that when regimen for chemotherapy is planned, we aim for the maximum tolerated dose, where we look for certain indications of toxicity to confirm the adequacy of the drug dose. Since, somewhere close to 90% of 5-FU is metabolised to a nontoxic di hydro 5 fluorouracil by DPD mostly in liver, the whole process is prone to saturation and the fact that the kinetics of 5-FU does not follow a linear curve worsens its cause even more.[10] So, a minor escalation in the dose or a downturn in conversion to di hydro fluorouracil can lead to an asymmetric rise of the drug and its toxic metabolites in the plasma. Sometimes other drugs accompanying 5-FU in the regimen too can interact with it in a detrimental manner for the patient. Methotrexate being one such example.[10]

URIDINE TRIACETATE: THE MOLECULE

Uridine triacetate (2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,4 (1H,3H)-pyrimidinedione, is an oral prodrug of uridine. It is an analog of pyrimidine, an acetylated uridine. Its weight is 370.3 grams/mole.[15] Depiction of structure in Figure 1.

Uridine triacetate is a drug approved for use in a rare congenital autoimmune medical disorder known as hereditary orotic aciduria (HOA) or orotic aciduria type I, with uridine-5-monophosphate synthase (UMPS) deficiency.[16,17] It is a very rare disorder with only about 20

cases being reported worldwide. HOA is characterised by anaemia of megaloblastic variety, fall in white blood cell count and orotic acid crystals in urine outlet pathway which may lead to its obstruction**.** It may even lead to delay in developmental milestones. It got FDA approval for use in HOA on September 4, 2015 following a clinical trial on 04 patients for a period of 6 weeks, prior to that the drug was designated orphan drug status for the same indication on 08 September 2013.[18]

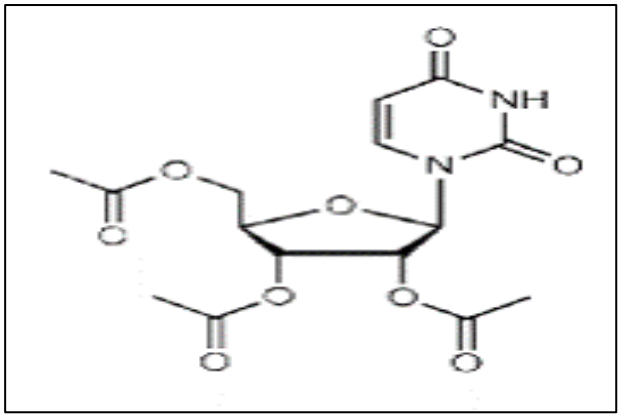

Figure 1: Uridine triacetate: structure.

Another potential use of the drug is as an antidote for toxicity or overdose of the anticancer drug 5-FU or its oral pro drug capecitabine. Uridine triacetate was given orphan drug status by FDA on May 01, 2009, for this indication.[19] The drug got approval by FDA on Dec 11, 2015 for use in fluorouracil toxicity or its overdose.[20]

URIDINE TRIACETATE-HOW IT WORKS?

Uridine triacetate after oral intake is being acted upon by esterase enzymes present in the peripheral circulation and happen to be non-specific. This leads to deacetylation of uridine triacetate and furnishing of free uridine.[15]

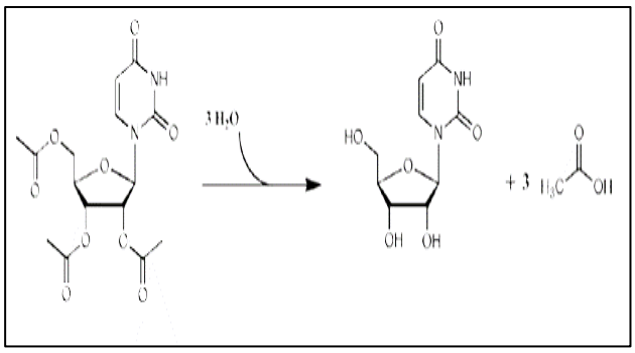

Figure 2: Uridine triacetate to uridine.

The 5-FU is converted into toxic metabolites by the enzymes of salvage pathway for pyrimidine. The metabolite 5-dUMP forms a complex with the enzyme thymidylate synthase, thus blocking this enzymes action, which prevents the Thymidine turnover. This thymidine plays an important role in synthesis, replication and repair of DNA.[2]

Another metabolite of 5-FU, fluorouridine triphosphate (FUTP) incorporates into the RNA which leads to the toxic effects of 5-FU. It has been noted that the amount of FUTP incorporation in the RNA is directly related to the extent of 5-FU a patient has been exposed to (either because of overdose or fast administration), which in turn reflects the amount of free FUTP available in body to produce the toxicity. What uridine does here is that it competes with these toxic metabolites after getting converted into uridine triphosphate (UTP) in the circulation, for inclusion into the RNA. Researchers believe that since uridine is not found in DNA and is found to be beneficial in case of toxicities caused by 5-FU, it is quite possible that the therapeutic effects of 5-FU is because of its action on DNA and the toxicities can be attributed to the entry of the metabolite in the RNA framework.[2,15] The drug uridine triacetate provides many folds higher levels of uridine in the circulation which takes about 2.5 hours to reach the peak plasma concentration. Its half-life also happens to be somewhere close to the same value.[15] While its absorption from stomach in the presence or absence of food has been unremarkable, it has been noted that it can cross the blood brain barrier.[15] Uridine is taken up by nucleoside transporters like transporter of pyrimidine specifically present in the gastrointestinal mucosal cells for this purpose. This transporter dependent movement is avoided by the pro drug uridine triacetate because of its high lipid affinity.[10] No microsomal enzyme induction or inhibition effects have been observed with the commonly studied enzymes in the in vitro studies, though uridine triacetate was found to act as a substrate, although a weak one for P-glycoprotein, so caution may need to be exercised if the drug is co administered with digoxin though no evidence can be produced in this regard for lack of in vivo information in humans.[15] Though oral administration of uridine triacetate did not show any detrimental effect on the product of conception in case of pregnant rats, its safety cannot be established in humans for want of enough evidence through studies. Similarly, in an absence of data regarding the secretion of uridine triacetate in human milk or its effect on breast milk production, any comment about the spectrum of safety in this regard is not possible.[15]

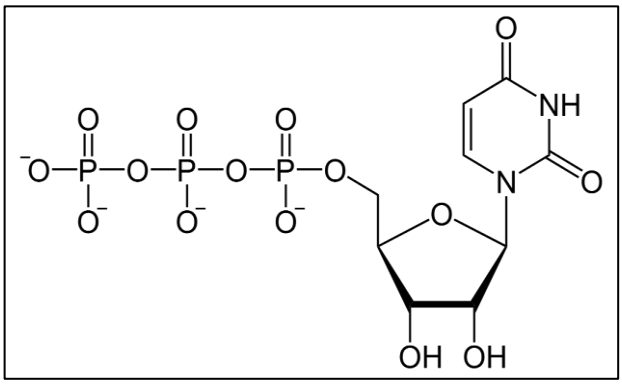

Figure 3: Uridine triphosphate.

Side effects and contraindications

Adverse reactions to uridine triacetate observed were vomiting, nausea and diarrhoea of which vomiting was the one seen in maximum, roughly 10% of patients and uridine triacetate was discontinued in 02 subjects because of the adverse reactions. No contraindications regarding the drug have been reported.[15]

Existing treatment options and other alternative drugs for toxicity

With 5-FU being a veteran amongst anticancer drugs in the war against cancer, introduced to the world by Charles Heidelberger in the year 1957, the hunt for an antidote towards its toxicity is not something new.[2]

Since 5-FU action is selective in action, based on the fact if a tissue is normal or cancerous, this makes it an able candidate for biochemical modulation studies. This study engages methods where one tampers with chemical pathway of metabolism of the drug in the tissue by a compound either synthetic or natural. While the final aim happens to be potentiating the anticancer abilities of the drug, suppressing the untoward effects of the drug or if possible, both, will be the best.[21]

Many agents have been tried in the past like interferon α, (phosphonacetyl)-L-aspartate (PALA), dipyridamole, uridine phosphorylase inhibitors, uridine, and a few others too. Out of these only uridines emerged as an agent that showed promise in terms of the ability to allow dose escalation and reverting the toxicities caused by 5-FU metabolites [22]

But uridine too, came with its share of problems, with a half-life of about 2 minutes and the liver metabolizing over 3/4th of uridine the level of uridine needed to be there in circulation to prevent toxicities of 5-FU or capecitabine was a minimum of 50 µmol/L. Whereas the body's production of uridine amounts to only about 6 µmol/L. The bioavailability of uridine too has been reported to be a meager 8%, so an oral dose of around 10 gm is needed to achieve a minimum therapeutic concentration of 50 µmol/L. But such large doses were found to induce nausea of severe grade and even diarrhea. Even the route of administration whichever was chosen to give uridine had its problems and limitations associated with it.[10]

So, amidst this hard-felt need for a suitable antidote uridine triacetate, uridine's pro drug was developed, which was supposed to be given orally. One of the advantages with it being, its lipophilic activities are higher in comparison to uridine so the need for a transporter for pyrimidine to get absorbed in the gastrointestinal tract was not there, leading to increased concentration of uridine in the circulatory system after conversion to uridine in the body, following deacetylation. This uridine is subsequently transformed into uridine triphosphate (UTP) which goes on to play a role in correcting and checking the toxicity.[10]

There have been studies that have even suggested that using uridine triacetate as an adjunct to 5-FU therapy may allow dose escalation of 5-FU up to 800 mg/m^2, this may lead to up to 5 times increase in the concentration of 5-FU available for action in the plasma leading to a marked decline in gastrointestinal toxicities and bone marrow suppression.[10]

EFFICACY OF URIDINE TRIACETATE IN CASE OF TOXICITIES

Following the analysis of a series of studies the American society of clinical oncologists (ASCO) finally reached a consensus regarding the dosing and duration of uridine triacetate administration in case of toxicity from 5-FU.[10] Information from a study done on patients exposed (accidentally) to 5-FU who were treated for toxicities with uridine triacetate and recovered fully was analyzed. A dosing regimen of 10 gm of uridine triacetate through the oral route, at an interval of 6 hours, 20 times was decided upon to be the best dosage regimen. It was also decided that the therapy with uridine triacetate should ideally begin after 8 hours of the patient's exposure to 5-FU and could be started up to 96 hours from the last exposure to 5-FU.[10] Clinical trials which took place comprising 135 patients followed this regimen only. For pediatric cases, the dose adjustment was made to 6.2 gm/m^2/dose to be given 20 times. (There were 04 such patients from infancy up to 7 years). Efficacy was studied in two trials, both being open-label, (n1=60) and (n2=75). Of the 135 patients recruited in the study, 112 had an overdose of 5-FU and 05 had that of capecitabine. The remaining 18 patients had developed serious toxicities to the normal dose regimen of fluorouracil.[15]

Out of 117 patients treated for overdose, 114 crossed the survival cut-off limit of 30 days. Similarly, 16 out of 18 patients treated for severe toxicities survived at the end of 30 days. Among 135 patients, 45 restarted their chemotherapy cycles within 30 days. Overall, more than 95% of patients successfully came out of the toxic exposure, the benchmark for which was kept to be survival at the 30th day or going back to the chemotherapy regimen before the lapse of 30 days. Out of the 05 patients who died of the toxicity, 02 received uridine triacetate after 96 hours of exposure to 5-FU had elapsed.[15]

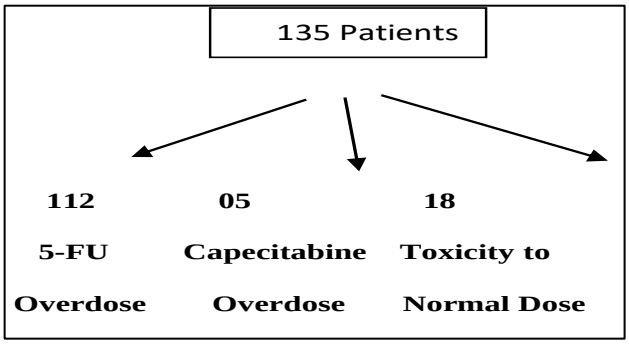

Figure 4: Patients who developed toxicities.

CURRENT STATUS

The drug uridine triacetate was approved by US FDA on December 11, 2015. Wellstat Therapeutics has been manufacturing the drug under the market name of Vistogard.[15]

While no comment can be made about the carcinogenicity of uridine triacetate due to the lack of long enough animal studies, the reproductive abilities were not affected in the case of rats for up to about half the recommended dose in humans.[15]

CONCLUSION

Uridine triacetate has shown enough promise to be used in the setting of a fluorouracil overdose or toxicity. The fact that 5-FU and capecitabine have been increasingly used in various types of cancers exposes more patients to a potential risk of toxicity caused by these drugs. Thus, for therapists to have an answer to these toxicities at their disposal can be very rewarding. Not to forget, the possibility of uridine triacetate allowing for fluorouracil dose elevation in its presence is being explored. In case, that aspect of uridine triacetate succeeds in seeing the light of the day, it would simply lead to the widening of the horizons for an ever-useful drug like 5-FU.

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