RECENT ADVANCES IN URINARY BLADDER CANCER CHEMOTHERAPY- THE MTOR INHIBITORS.

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ABSTRACT

Mtor inhibitors are new drugs used in the transplant medicine as immunosuppressants. These drugs have been tried in Renal Cell Carcinoma and Urinary bladder cancer. These molecules have shown encouraging results in treatment of urinary bladder cancers as single agent as well as in combination with cisplatin and gemcitabine.

KEYWORDS: Mtor, renal cell carcinoma, urinary bladder carcinoma, cisplatin, gemcitabine.

INTRODUCTION

An upsurge of advances in the management of bladder cancer has rapidly occurred over the past 2 years. Some of the drugs used in urinary bladder cancer chemotherapy have been in use for more than 30 years and show reduced effectiveness and high recurrence rates. There was a great need for the development of a new drug which can not only reduce the recurrence rate of bladder cancer but can induce to cure of this dreaded disease.

Drugs used

At present mainly, three drugs are available in this group:

1. Sirolimus
2. Everolimus
3. Temsirolimus.
Sirolimus: It is also known as Rapamycin, a macrolide compound that is used to coat the coronary stents, prevent organ transplant rejection and to treat rare lung disease and lymphangioleiomyomatosis.[8,9,10] It has immunosuppressive functions in humans and is specially used in preventing the renal transplant rejection. It inhibits activation of T cell and B cell by reducing their sensitivity to Interleukin-2 through mTOR inhibition.[11]

It is produced by the bacterium Streptomyces hygroscopicus and was isolated for the first time in 1972 by Surender Nath Saigal and colleagues from samples of Streptomyces hygroscopicus found on Easter Island.[12,13] The compound was originally named as ‘Rapamycin’ after the native land of island-Rapa Nui.[9] Sirolimus was initially developed as an antifungal agent. However, this use was abandoned when it was discovered to have potent immunosuppressive and anti-proliferative properties due to its ability to inhibit mTor. It was approved by USFDA and is marketed under the trade name- RAPAMUNE by Pfizer.

Everolimus
It is the 40-0-2-hydroxylethyl derivative of sirolimus and works similarly to sirolimus as an inhibitor of mammalian target of rapamycin (Mtor).

It is currently used as an immunosuppressant to prevent the rejection of transplants and in the treatment of renal cell cancer and other tumours. Much research has also been conducted on everolimus as targeted therapy for use in a number of cancers.

It is marketed by Novartis under the trade name Zortress (USA), Certican (Europe and other countries) in transplantation medicine and as Afitor (general tumours) and votubia (transitional cell carcinoma) in oncology. Everolimus is also available from biocon, with the brand name Evortor.[14,15]

Temsirolimus
(Code name CCI-779): It is an intravenous drug for the treatment of renal cell carcinoma (RCC) developed by Wyeth pharmaceuticals and approved by USFDA in the late May, 2007 and European Medicines Agency (EMA) in November, 2007. It is a derivative and prodrug of sirolimus and is available commercially as Torisel.[16,17]
MECHANISM OF ACTION
Preclinical studies have shown that PTEN loss enhances sensitivity to mammalian target of Rapamycin (mTor) inhibitors because of facilitated PI3K (Phosphatidylinositol-3 kinase)/Akt activation and consecutive stimulation of the mtor pathway. In patients of advanced transitional cell carcinoma (TCC) treated with mTor inhibitor- everolimus, PTEN loss was, however, associated with resistance to treatment.[7]

The mechanistic or mammalian target of Rapamycin (mTor) is a major singling pathway in eukaryotic cells belonging to the PI3K related kinase family of the serine/threoneine protein kinase. It has been established that mTor plays a central role in cellular processes and has been implicated in various cancers, diabetes and in the aging process with very poor prognosis. Inhibition of the mTor pathway in the cells may improve the therapeutic index in cancer treatment.[1] Housede N and Pourquier P have mentioned that the genetic background of urothelial cancers of urinary bladder, revealed chromosomal alterations that are not seen at the same level in other types of cancers. This is especially the case for the mutations of genes involved in the PI3K/AKT/mTor signaling pathways that occupies a major place in the etiology of these tumours.[3]

RESULTS FROM DRUG USE
These drugs work in isolation and in conjuction with non-mTor inhibitors like cisplatin and gemcitabin. The non-muscle invasive cell line- 5637exhibits a small alteration in the mTor and AKT phosphorylation after exposure. Also, there is small inhibition of cell proliferation. Gemcitabin with everolimus or temsirolimus also give promising results, as an antiproliferative effect was observed when drugs were co-associated, in particular on the 5637 and HT1376 cell lines. Cisplatin associated with Everolimus in conjuction with gemcitabine or cisplatin might have an important role in urinary bladder cancer treatment depending upon the tumour grading.[5]

In another study by Pinto-Leite R etal[6] cytotoxic action of temsirolimus using 3 established human bladder cancer cell lines was analyzed and assessment whether temsirolimus potentiate the anticancer activity of gemcitabin and cisplatin was studied. Temsirolimus (T24, and 500, 1000, 2000 and 4000 Nm and cisplatin (2.5 microgram/ml was given to 5637, and HT1376, T24 and HT 1376 Bladder cell lines. Cell proliferation, autophagy, early apoptosis, and cell cycle distribution were analysed after 72 hour period. The expression of
mammalian target of rapamycin baseline- Akt, and their phosphorylated forms, before and after treatment with temsirolimus was evaluated by immunoblotting.

Their results showed that Temsirolimus slightly decreased the bladder cell proliferation in all 3 cell lines. No significant difference in expression of mammalian target of rapamycin, Akt and their phosphorylated forms because Temsirolimus exposure were found in 3 cell lines as part of combine regimen along with gemcitabin, and specially with cisplatin , it was more pronounced anti proliferative effect. This pattern of response was similar to other parameters analyzed (increased autophagy and apoptosis). Also in combined regimen, an enhanced cell cycle arrest in the G0/G1, phase was observed. In this study, the non-muscle invasive 5637 bladder cancer cell line was most sensitive to both combinations.[6]

Fasolo A and Sessa C in their review article concluded that Temsirolimus and everolimus can be used for treatment of metastatic renal cell carcinoma, temsirolimus alone for mantle cell lymphoma and everolimus for pancreatic neuroendocrine tumors. All these rapaloges are currently been evaluated in phase III studies in several tumours. However, in vitro and in vivo preclinical studies have shown a significant anti-proliferative activities against a broad panel of tumors and a favourable safety profile, with disease stabilization or even tumour regression, either as a single agent or in combination.[2]

REFERENCES
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