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Can intravesical application of paracetamol benefit the chemotherapy treatment of bladder cancer?

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ABSTRACT

Bladder cancer is one of the most common urogenital tumors. Its prevalence is increasing worldwide, especially men. The cyclooxygenase-2 (COX-2) enzyme has been shown to increase in bladder cancer and has a direct relationship with tumor progression. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce the growth of the tumor by inhibiting the COX-2 enzyme. NSAIDs have other effects unrelated to COX that provide anticancer properties. Also, similar to NSAIDs, anticancer effects of paracetamol have been shown in many studies. Therefore we hypothesize intravesical paracetamol application will have beneficial effects in the treatment of non-muscle invasive bladder cancer (NMBIC).

Introduction

Bladder cancer is the 9th most common type of cancer and the 2nd most common urogenital cancer with a rising number of cases around the world. Although the reason is unclear, it is more prevalent in men compared to women (8.9% and 2.2% respectively) [1]. 75% of all bladder cancer cases are non-muscle invasive bladder cancer (NMBIC). 25% of all cases are muscle invasive bladder cancers (MIBC). The treatment procedures for MIBC are radical cystectomy and standard chemotherapy applications especially with platinum derivations. Transurethral tumor resection, intravesical chemotherapy and immunotherapy form the basis of treatment for NMBIC. Despite all these treatments, approximately 21% of NMIBC patients develop invasive cancer within 4 years and approximately 14% of these patients pass away [2]. The survival rate for 5 years is 90% for patients with NMBIC and 50% for patients with MIBC despite treatments [3]. Therefore, it is crucial to develop different treatment methods and new agents that can be used for treatment of bladder tumor.

Cyclooxygenase-2 (COX-2) levels increase which can be induced by various factors has been shown in bladder tumor and many other types of cancers [4,5]. COX-2 enzyme has different effects on tumor progression. For example, COX-2 enzyme levels show a direct proportion with cell proliferation and progression in tumors while apoptosis decreases at a similar rate [6]. It is thought that PGE_2, which is one of the products of the enzyme, is responsible for the effects COX-2 has on tumors. PGE_2 is related to several intracellular pathways such as phosphoinositide-3-kinase/akt (PI3K/AKT), protein kinase A (PKA), mitogen activated protein kinase (MAPK) [7]. Therefore, non-steroidal anti-inflammatory drugs (NSAIDs), both selective COX-2 inhibitors and non-selective COX inhibitors, have been seen as potential anticancer drugs and in many studies these drugs have been shown to reduce proliferation, increase apoptosis, and reduce invasion and angiogenesis in tumor cells [8].

Paracetamol is a globally common agent used as an analgesic and antipyretic. It shows its effects by inhibiting COX enzymes similar to NSIADs [9]. There are many studies that support the claim that paracetamol has anti-cancer properties similar to NSAIDs. For example, it has been shown that it caused cell death by nuclear factor kappa B (NFkB) regulation in a study conducted on human neuroblastoma cell culture [10]. Furthermore, it was found in the study of breast cancer cells that the effect of chemotherapeutic agents was increased [11]. In addition epidemiological study, that on individuals who regularly use NSAIDs with paracetamol as a part, the rate of suffering from glioblastoma is lower compared to non-user individuals [12].

Hypothesis

In this context, application of intravesical paracetamol in conjunction with immunomodulatory Bacillus Calmette-Guerin (BCG) toxin and other chemotherapeutic drugs can prevent relapses and prolong life span, especially on patients suffering from MIBC. This practice can yield more effective results compared to the systemic procedure and can

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bring out different anti-cancer properties of paracetamol more effectively. The fact that intravesical paracetamol can influence tumor tissue with higher concentrations compared to oral or intravenous (IV) application can increase the antitumor activity or can realize different formulations of paracetamol for intravesical application. It can be fairly beneficial in terms of preventing a difficult procedure for creating a new drug and realizing an effective treatment procedure.

Validity of hypothesis

There are many factors playing a role in pathogenesis of bladder cancer. Most important of these factors is smoking and it is seen in approximately 50% of cases. Additionally, polycyclic hydrocarbons related to environmental pollution and dietary habits and drinking water with high chlorine levels forms other risk factors. Furthermore, genetic factors have an important role at progression of bladder tumor [13]. BCG is obtained by weakening Mycobacterium bovis and used intravesically for treatment of intermediate and advanced level of NMBIC. Although the impact mechanism is unclear, it increases the secretion of several different cytokines like tumor necrosis factor alpha (TNF-α), interleukin 2 (IL-2), interferon gama (IFN-γ) by stimulating toll like receptors (TLR) in tumor cells [14,15]. In order to increase the effectiveness of BCG in the treatment of bladder cancer, intravesical combinations with different drugs have been examined in recent years. For example, in a study conducted on rats, it has been concluded that the intravesical application of curcumin in conjunction with BCG reduced tumor size, even though it is statistically insignificant, and can be a hope for treatment [16]. In a similar study it was concluded that neoplastic lesions of 70% of rats showed remission after intravesical application of platelet rich plasma in conjunction with BCG [17].

In several studies conducted on humans it is demonstrated that COX-2 enzyme increased in transitional cell carcinoma and the increase is comparatively higher in high grade tumors, which indicates that in can be a useful prognostic marker [18]. In another study conducted on humans, it was demonstrated that PGE_2 receptor EP1 can be used as a prognostic factor on patients with NMBIC and positive outcomes on cancer treatment can be achieved by regulating EP1 receptor [19]. In in vivo studies conducted on NMIBC patients it has been found that oral celecoxib contributes to cancer chemotherapy [20,21]. Furthermore, the risk of bladder cancer formation in humans receiving various NSAIDs such as ibuprofen has less risk than those who do not use them [22]. Similar experimental studies have demonstrated that naproxen and the selective COX inhibitor licofelone increased apoptosis, reduced proliferation and inhibited tumor growth in bladder cancer [23].

It has been suggested that NSAIDs have anti-tumor effects by COX inhibition as well as COX-independent effects and these effects contribute to anticancer properties. For example, it is shown that some NSAIDs inhibit cell proliferation by directly impacting several transcription factors like IKKb, Erk, p38 MAPK, Cdks cellular kinases. But, it is determined that these effect are not seen on all NSAIDs and that there are several differences between drugs. For instance, although indomethacin has been found to cause PPAR activation, it has no effect on activation of factors such as NF-kB and Erk and Cdk. However, it has been shown that aspirin has not such an effect [24]. In a study conducted on in vitro glioblastoma cell culture with specific COX-2 inhibitor celecoxib, it is shown that the antiproliferative effect is related to cyclin A and cyclin B inhibition similar to these studies [25,26].

Even though paracetamol is seen in the other analgesic and anti-inflammatory drug group due to its weak anti-inflammatory property, it is fairly effective at reducing pain and body temperature and its adverse effects especially like gastrointestinal tract are lower than NSAIDs. However paracetamol can lead to hepatotoxicity especially with high doses. Paracetamol is metabolized mainly with glucoronic acid and sulphate (63%, 34%) in the liver. A very small portion (< 5%) is turned into N-acetyl benzoquinoneimine (NAB) by oxidative metabolism with CYP450 enzyme systems. Under normal conditions, this obtained metabolite is turned in to cysteine and mercaptopurine with glutathione. However, if paracetamol is taken on high doses NAB levels rise and glutathione deposits in hepatocytes decrease. Unmetabolized NAB connects to cellular proteins, disrupts hemostasis, leads to caspase activation and cellular apoptosis and eventually causes liver failure [27]. However, paracetamol increases reactive oxygen species (ROS) and has toxic effects especially on brain and kidneys [9,28]. In studies with various cell cultures has been shown that paracetamol decrease cell proliferation. For example, on studies conducted with rat C6 and human U138-MG glioblastoma cells, it is determined that depending on the dose, paracetamol lowered apoptosis and inhibited proliferation on both types of glioma cells [29]. Paracetamol lowered cell proliferation in human mesenchymal cell culture by causing c-jun terminal kinase (JNK) and p38 phosphorylation [30]. On a different study conducted on hepatoma cell culture, it is concluded that paracetamol caused an increase in caspase-3 and DNA fragmentation and apoptosis in these cells [31]. We have two different studies, in vivo and in vitro, in which we investigated anticancer properties of paracetamol. On the in vitro study conducted on human cervix HeLa cell culture we have determined that paracetamol lowered cell proliferation depending on dose and incubation time [32]. Second study was conducted in vivo with paracetamol, indomethacin and metamizole on rats with C6 glioblastoma cell culture. In this study there was not any difference between tumor tissue and normal brain tissue in terms of COX-1 and COX-2 enzyme levels, but COX-3 enzyme level was meaningfully higher on tumor tissue. Paracetamol and indomethacin meaningfully lowered the increase in COX-3 levels compared to the control group. Indomethacin and paracetamol meaningfully reduced tumor size compared to the control group with a higher level on group with paracetamol [33]. On another in vitro study conducted with glioblastoma, which is not yet published, we have determined that paracetamol inhibited glioblastoma cell proliferation by COX-2 and several different mechanisms. All of these results show that paracetamol can have anticancer potential, due to COX enzyme or others mechanism independent from COX above mentioned.

Conclusion

By intravesical addition of several commonly used drugs like paracetamol, which have been shown to have different effects on tumors, to the standard treatment protocol in bladder cancer, apoptosis on tumor cells can be increased, tumor proliferation can be decreased, life span of patients can be prolonged and paracetamol can be used as an effective anticancer agent.

Declaration of Competing Interest

There is no conflict of interest

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