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Prevention of Urinary Bladder Cancer - The Trail Less Trodden

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ABSTRACT

Though the pathogenesis of urinary bladder cancer is now well known, the exact aetiology of this disease is still in darkness. The advances in the management of bladder cancer have focused only on early identification and treatment of the illness since stage of disease at the time of diagnosis is a critical factor determining the outcome of treatment. Though primary chemoprevention of any disease aims at decreasing the incidence, secondary objectives like reducing treatment-related adverse events, cutting down the cost of treatment and bringing down the mortality due to the disease are also of concern. Chemoprevention of bladder cancer is a path less trodden. The primary reason for this lacunae has been the lack of identification of specific agents useful for this purpose. This article reviews the experimental and epidemiological data available from 1998 to 2024 on the effectiveness and safety of various nutritional and other agents proposed to be useful for bladder cancer chemoprevention to reduce the incidence of this cancer and/or slow down the disease progression. The results of the review show that no single agent has been categorically proved to be the best for chemoprevention of bladder cancer as of now. It may be ideal for patients who are at higher risk of contracting bladder cancer to adopt feasible chemopreventive measures which could potentially retard the onset or further course of disease including life style modifications and quitting smoking habits.

Introduction

Urinary bladder cancer (BC) currently ranks 9th in incidence globally[1] with the incidence rates varying over the years. Though incidence and mortality of BC has decreased in some registries reflecting the decreased impact of causative factors[2], the incidence ranks still higher in Europe and North America compared to the rest of the world[3]. The need for accurate diagnosis, continuous surveillance, repeated treatment sessions together with the aggressive management of invasive disease makes BC one of the most expensive tumors in terms of total medical care expenditure.

The urothelial type of BC (UBC) remains the commonest variety with other histological forms like squamous carcinoma, adenocarcinoma, neuroendocrine carcinoma etc. constituting less than 10 % of cases. The UBC is further subdivided into high grade (HG) and low grade (LG) varieties[4]. Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). The incidence of superficial (Non Muscle Invasive UBC, NMIBC) is still higher in younger patients (< 40 years of age)[5]. The behaviour of advanced staged UBC (Muscle Invasive UBC, MIBC) is radically different from that of NMIBC and warrants aggressive treatment with extensive surgeries concomitant with chemo-radiation. The results of treatment of BC is greatly dependent on the grade and stage of tumour.

The current diagnosis of BC is based on clinical history and cystoscopic evaluation (followed by resection when needed), ultrasound scan (USS), magnetic resonance imaging (MRI), computerised tomography (CT) scan and urine cytology. Cytological examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG tumours (84%), but low sensitivity in LG tumours (16%)[6]. The sensitivity of cytology in carcinoma in situ (CIS) detection varies from 28–100%[7]. Therefore, the current role of cytology is still restricted and more sophisticated non-invasive tests are required in order to obtain more information on the biology of tumors, particularly in the early stages of the disease and when the grade of the tumor is low.

Urinary bladder cancer shows a significantly higher incidence in males, in the ratio 3.5:1 compared to females. The incidence has been identified to be even more alarmingly high in Indian population with male to female ratio of 8.6:1[8]. Women are more likely to be diagnosed with muscle invasive UBC than men (85.2% and 50.7% respectively) and women with UBC are approximately twice more likely than males to die from this disease[9,10,11,12]. These studies also highlight that gender differences exist in the timelines promptness of evaluation for hematuria in patients with UBC; with females often getting delayed in the diagnostic evaluation of hematuria. Further, even when men and women consume tobacco at comparably high levels, the risk of UBC among women was found to be 30-50% higher than men[13]. The gender gap in environmental carcinogen exposure, the sex steroid hormone pathway, metabolic enzyme activity and differences in implementation of evaluation programs are all possible contributing factors accounting for the observed demographic trends in UBC.

Urinary bladder cancer has been traditionally associated with several environmental and occupational causative agents. BC, like prostate cancer, has a protracted course and hence may be well suited for preventive strategies[14]. The majority of cases, despite being detected at an early stage are subject to recurrences and hence this is another aspect where some of the preventive measures would come to fore.

Though there is paucity of literature on the specific measures to be adopted for chemoprevention of BC, there is a mini-review[15] which highlights exposures that are associated with higher risk of BC, summarizes the evidence for each association and suggests strategies to decrease risk at both individual and population levels.

In an effort to slow the progression of disease or lower the incidence of BC, a variety of nutritional and other agents are proposed for use in BC

chemoprevention. This article reviews the experimental and epidemiological data on the efficacy of various agents for BC chemoprevention, available in Medline and Pubmed Search from 1998 to 2024.

Dietary Factors

1. WATER

Theories of the protective role of water were proposed as early as in 1954. The 'Urogenous' theory believed that a higher water consumption would lead to more urine production thereby resulting in a dilution effect of toxins which come in contact with the mucosa[16]. In one of the largest prospective studies done[17], water consumption was found to be inversely related to the risk of fluid consumption. Subjects who consumed more than 2531 ml (highest quintile in the study) had a 49% lower incidence of bladder cancer than those who consumed less than 1290 ml (lowest quintile). In the same study, when water consumption was labeled as a continuous variable, there was a 7% decrease in incidence of bladder cancer for every increment of 240 ml in daily water intake.

It is interesting to note that water accessible to most of the people in a given community would be contaminated with chemicals that include chlorination byproducts and arsenic which themselves can cause BC when consumed in large quantities[18]. Unfortunately, chlorination continues to remain as the most commonly used water disinfectant globally[19]. This has led to prospective studies to better define the association between chlorination and the development of BC. A Swedish prospective study[20] assessed the relation between Trihalomethanes (THM), the chlorination by-product usually found in highest concentration[21] and development of BC. The THM levels in drinking water were quantified and 58,672 participants were categorized into non exposed, low and high exposure groups. After a follow up period of 16 years, no significant association was noted between the THM levels and development of BC. Therefore the actual protective nature of water consumption in BC is still debated.

Several meta-analyses have been conducted which have looked into the nature of association between water intake and development of BC[22,23,24]. The findings showed that the effect varied with geographical location, time at which study was conducted and the sex of the individual. High fluid intake seemed to be a risk factor for BC in European male and American residents but this had a protective effect in Asian population (who have a habit of boiling water routinely). Therefore, the advice to have an average intake of 2-3 L of water per day would be the best course of action for prevention of BC.

2. FRUITS AND VEGETABLES

Most fruits and vegetables contain or are digested to produce antioxidants the bulk of which are eventually excreted through urine[25]. Phytochemicals and extracts derived from avocados exhibit anticarcinogenic properties, such as apoptosis induction, cell cycle arrest, antioxidant activity and inhibition of cell proliferation, in various cancer cell lines[26]. The outer layer (peel) of the pomegranate contains high concentration of phenolics, flavonoids, ellagitannins (mainly punicalagin) and proanthocyanin compounds all of which were found to be inhibitory to BC cells[27].

Flavonoids, which are secondary metabolites, constitute a subgroup of polyphenols found in various sources such as fruits, vegetables, chocolate, flowers and tea. Several flavonoids have been shown to inhibit the proliferation and migration of BC cells, including curcumin, which has been found to induce apoptosis and repress bladder tumor growth in vitro and in vivo[28]. Genistein, an isoflavanoid predominantly found in soybeans, has been found to have anti-cancer effects via the mediation of apoptotic cell death associated with G2/M arrest of the cell cycle in human urinary bladder carcinoma T24 cells[29]. A similar protective effect has also been noted with cranberry juice courtesy flavonoids like quercetin 3-O-galactoside[30].

3. VITAMINS

Various food sources, such as cereals, meat, fruits, and vegetables contain a rich abundance of B-

group vitamins, including vitamins B2, B6, B12 and Folate, also known as vitamin B9. These vitamins play crucial roles in essential cellular functions, like the metabolism of macronutrients, the 'energy pathways' and nucleic acid synthesis pathways and also breaking down of tryptophan metabolites in the urine. These B Group vitamins have also shown to have a protective effect on the development of BC[31]. Milk, which is rich in these vitamins, particularly B12 has also shown to have similar properties[32]. However, retinoids including vitamin A, fenretinide and etretinate have all proved to be not effective as primary chemopreventive agents of any clinical value.

Vitamin D has established anticancer properties, including the regulation of anti-angiogenesis and pro-apoptosis mechanisms[33]. In the setting of BC, it has demonstrated inhibitory impact on migration and infiltration in human BC cell lines[34]. However the hypothesized protective effect of vitamin D could not be confirmed in a meta-analysis which specifically examined the role of vitamin D intake from both diet and supplements[35]. A similar protective association has also been seen with Vitamin E and to a lesser extent with Vitamin C.

4. MEAT

Increased consumption of red and processed meat was found to be a notable contributing factor for BC, resulting in a corresponding increase in cancer risk by 17% and 10% respectively. The increased susceptibility is proposed to be due to the presence of N-nitroso substances which potentially cause BC[36]. Therefore reducing the intake of meat and meat products in the food can be protective of BC.

Drugs

1. STATINS

The presence of chronic hyperlipidemia is a risk factor for several cancers including BC with a stronger association in younger men[37]. Statins work by inhibiting the key enzyme in the mevalonate pathway - HMG CoA Reductase. Statins are also known to obstruct Ras/Rho pathways, thereby curtailing various cancer-promoting signaling routes[38]. There is some evidence to show that selected statins (especially Rosuvastatin) may have a protective effect from BC[39].

2. ASPIRIN

Non-steroidal Anti Inflammatory Drugs (NSAIDs) act by inhibiting the COX pathway which promotes inflammation. It is proposed that COX-2 may play a role in progression of BC by creating a pro-inflammatory state and reducing apoptosis[40]. Aspirin should therefore have a protective effect through this interaction. But aspirin has also been shown to interact through several other pathways like AMP-activated protein kinase, mechanistic target of rapamycin complex 1, p21Waf1 and RB1 in the setting of other cancers like breast cancer[41] and neuroblastoma[42]. A meta-analysis showed that aspirin use had a strong relevant association with decreased incidence of BC though progression, recurrence and survival of patients with proven BC were not affected by consumption of aspirin[43].

3. THIAZOLIDINEDIONE DRUGS

The thiazolidinedione class of oral hypoglycemic agents were once a popular group of drugs used in the treatment of type 2 diabetes mellitus. The PROactive (Prospective pioglitazone clinical trial) study in 2005 showed a significantly higher number of BC cases in those taking pioglitazone when compared to placebo[44]. However since then, there have been several studies that have looked into this association. It has been found that the association is specific to pioglitazone. Other congeners like rosiglitazone have been found not to have such an association[45]. Pioglitazone acts by activation of PPARα/γ. PPARα/γ activation in rat models has been shown to increase the expression of carcinogenic biomarkers in the bladder, which has not been observed with the selective activation of PPARγ[46]. Rosiglitazone has no such BC association courtesy its selective action on PPARγ.

4. OTHER COX 2 INHIBITORS

There are studies which have extrapolated the role of COX-2 inhibitors in preventing BC. Okamoto et al.[47] examined the cytotoxicity of Etodolac against three human BC cell lines, T24, 5637, and KK47

and performed quantitative reverse transcriptase-polymerase chain reaction to measure the mRNA expression of COX-2, and E-cadherin. It was observed that Etodolac showed significant cytotoxicity only to T24 cells, which expressed the greatest level of COX-2 mRNA and the lowest level of E-cadherin mRNA among the three cell lines. Etodolac also increased the E-cadherin mRNA expression in T24 cells in vitro. Etodolac also suppressed tumor growth and induced E-cadherin expression and cell apoptosis in a T24 tumor xenograft mouse model. Therefore, Etodolac, which exhibited antitumor activity and induced E-cadherin expression in bladder cancer cells might be useful for clinical treatment and prevention of bladder cancer, especially in poorly differentiated bladder cancer with high COX-2 and low E-cadherin expression.

Rofecoxib treatment has also been found to significantly reduce the incidence of preneoplastic. lesions/bladder tumors. Comparing the incidence of neoplastic lesions in mice treated with Rofecoxib and N-butyl-N-(-4- hydroxybutyl)-nitrosamine (BBN) (22/56, 39.3%) and mice treated only with 0.1% or 0.01% BBN (32/57, 56.1%), a protective role of Rofecoxib on the BBN tumor induction was observed (P=0.024)[48]. These findings suggest that Rofecoxib provides a therapeutic defence against bladder carcinogenesis and confirmed that the FHIT (Fragine Histidine Triad) knock-out mouse is a suitable system to study in vivo bladder carcinogenesis.

Lifestyle Factors

1. EXERCISE AND PHYSICAL ACTIVITY

Physical activity has been associated with biological pathways like enhanced immune function, reduced chronic inflammation, detoxification of carcinogens, enhanced DNA repair, modified cell proliferation and apoptosis[49]. Exercise also has an indirect effect of weight reduction which protects against the development of BC. One meta-analysis[50] and a pooled analysis[51] showed a decreased risk of BC associated with physical activity. The meta-analysis also showed that increasing duration of physical activity also had decreasing risk of BC.

2. SMOKING

Tobacco smoking has long been recognized as one of the most important risk factors for BC. Meta-analysis done in 2000[52] and 2016[53] showed a dose dependent association of smoking with BC; current smokers having more than threefold risk and reformed smokers having a twofold risk. The effects were also dependent on cumulative dose acquired through a lifetime[54]. Furthermore the effects of smoking also affected the outcome of patients being treated for BC. In a prospective study of 1472 patients with NMIBC[55] higher pack-years was associated with a higher risk of recurrence. The effects were seen in a dose dependent manner as shown in most studies.

There is an interesting study[56] to investigate the awareness of smoking as a risk factor for BC among bladder cancer patients. This was a substudy of a prospective, randomized, multicentre phase 3 trial (FinnBladder 9, NCT01675219), wherein the data were collected at baseline and after 12 months of follow-up between 2012 and 2020. It was observed that 44% of patients were uncertain if smoking was a risk factor for BC. However, patient awareness of the fact that smoking cessation reduces the risk of BC recurrence increased from 86% to 92% after 12 months of follow-up (p=0.038). Surprisingly, elderly patients and patients with recurrent BC had significantly lesser knowledge about the effect of smoking on BC, its recurrence, progression and mortality.

The effects of marijuana smoking were, however, interestingly different with regards to the development of BC. A study[57] including 84,170 participants on 11 year follow up period showed that there was a 45% decreased incidence of bladder cancer in marijuana-alone consumers when compared to tobacco-alone consumers. Limitations included participation and response biases, lack of evaluation of other BC risk factors, lack of assessment of the time course between cannabis use and diagnosis and no reported average cannabis use[58].

3. ALCOHOL

Being a globally consumed beverage, alcohol use has been the subject of several studies attempting

to prove an association with development of cancer. Although there are several well known cancer associations with alcohol[59], the association of this beverage with BC remains inconclusive. The confounding effects of smoking often make matters more complicated. Meta-analyses have shown conflicting results with some showing no association[60,61] whereas some others showing an association with specific types of liquor and male sex[62]. The result from meta-analysis done in 2010[63] showed that beer and wine consumption had an inverse dose-risk relation, though this was not replicated in any of the other meta-analysis reports. The byproducts of alcohol metabolism, especially the aldehyde compounds are known to interact with enzymes involved in DNA repair and result in carcinogenesis[64]. A meta-analysis done in 2021[65] was also unable to show a definite association with alcohol consumption, though a relationship was noted among those who consume alcohol from liquor or spirits.

There is an interesting research article[66] which summarizes key dietary factors, types of physical activity, and smoking in relation to BC incidence and discusses the potential public health implications for formalized smoking cessation programs among recently diagnosed patients. According to these authors, population-based research in BC was expanding and would be a vital resource for patients and their treating physicians to learn how altering one's lifestyle could result in the best possible outcomes.

Hormonal Factors

It is possible that there could be gender specific differences in the degradation of carcinogens at the molecular level[67]. Gender variations in hydroxylation, acetylation and glucuronidation pathways including various enzymes such as uridine-diphosphoglucoronosyl transferase (UGT) and NAT-2 play an essential role in the degradation of aromatic amines, contributing to carcinogenesis including BC. Glutathione-S-transferase M1 (GST M1) is an enzyme that degrades certain carcinogens by conjugation to glutathione[68]. It is worthwhile studying whether there are gender differences in UGT expression, NAT-2 status and GSTM1 expression contributing to the sex specific differences in BC susceptibility.

The androgen receptor (AR) is a steroid hormone receptor activated by the androgens namely testosterone and dihydrotestosterone (DHT)[69]. In the absence of androgens, signaling initiated by other receptors like epidermal growth factor receptor (EGFR) may facilitate the activation of AR. It has been found that in UBC, the AR expression decreased with increasing pathological stage, with 88.9% of pTaUBC and 0% of pT3UBC expressing the AR respectively[70]. In addition, co-regulators of the AR enabling the formation of the AR transcriptional complex have been found to be expressed in 85-100% of UBC specimens[71]. Additionally, high risk UBC might lose the expression of 5α reductase leading to decreased conversion of testosterone to the more potent DHT[72]. The increased androgen-dependent susceptibility of the urothelium to carcinogens, impaired carcinogen degradation by androgen-dependent pathways, or direct androgen-induced carcinogenesis are some of the molecular mechanisms by which androgens contribute to the development and progression of UBC[73]. A detailed review on the clinical and therapeutic implications of sex steroid hormone receptor status in UBC has been published by Moorthy HK et al.[74].

Some studies have reported that androgen receptors could influence various other signaling pathways also by interacting with β catenin, cyclin-d and EGFR to promote carcinogenesis of aggressive biologic behavior[69,75,76,77].

The expression of estrogen receptor β (ERβ) has been found to be increasing with advancing pathological tumor stage and higher grading[78]. 53% of pTa UBC and 75% pT4 tumor as well as 58% of WHO grade 1 and 2 tumors and 70% of grade 3 tumors were seen to express ERβ respectively. In contrast, the ERα was rarely expressed in the urothelium and not associated with UBC showing progressive behaviors[79]. However, there is limited

knowledge on the role of progesterone receptor A which has been found to be expressed in the urethral squamous epithelium in UBC carcinogenesis[80]. In vitro and animal experiments have suggested the usefulness of Tamoxifen, an anti-estrogen in reducing UBC incidence following carcinogen exposure[81].

Loss of X linked lysine demethylase 6A (KDM 6A), a sexually dimorphic gene, increased UBC risk in female mice and mutations or reduced expression of human KDM 6A predicted poor prognosis of female UBC patients[82].

Trilla-fuertes L et al examined the luminal and basal cell groups independently in an effort to use computational analysis to characterize muscle invasive bladder tumors at the molecular level[83]. Flux balance analysis revealed that basal tumors were highly proliferative, making them suitable candidates for neo adjuvant chemotherapy. The luminal tumors, however, were good candidates for therapy with androgen receptor inhibition.

The results of these studies on the role of sex steroids and receptors on BC carcinogenesis open new vistas in the possible usage of agents which can counter the effect of these hormones, and thereby could be effective for prevention and therapy of clinical BC in future.

Genetic factors

Various genetic factors influencing bladder carcinogenesis and the role of genetic manipulations in reducing the risk of BC have been the hot topic of study by various researchers, at least in the experimental set ups.

Koutros S et al.[84] identified new genetic markers that provided biological insights into the genetic causes of BC. Multiple novel bladder cancer susceptibility loci (6p.22.3, 7q36.3, 8q21.13, 9p21.3, 10q22.1, 19q13.33) as well as improved signals in three known regions (4p16.3, 5p15.33, 11p15.5) were identified, bringing the number of independent markers at genome-wide significance to 24. The 4p16.3 (FGFR3/TACC3) locus was associated with a stronger risk for women than for men (p=0.002). BC risk was increased by interactions between smoking status and genetic variants at 8p22 (NAT2; multiplicative p value for interaction [pM-I] = 0.004), 8q21.13 (PAG1; pM-I = 0.01), and 9p21.3 (LOC107987026/MTAP/CDKN 2A; pM-I = 0.02). The PRS (Polygenetic Risk Score) based on the 24 independent GWAS (Genome-wide Association Studies) markers (odds ratio per standard deviation increase 1.49, 95% confidence interval 1.44–1.53) revealed approximately fourfold difference in the lifetime risk of BC (e.g., 1st vs 10th decile) for both smokers and nonsmokers. Therefore they postulated that these genetic risk factors combined with lifestyle risk factors, such as smoking, could hold the key for future preventive and screening strategies for BC.

The Ubiquitin-proteasome system (UPS) is known to participate in multiple cellular events. The deubiquitinating enzyme, USP2 (ubiquitin-specific protease 2) is involved in the vasculature remodelling process associated with BC[85]. USP2 was significantly upregulated in BC tissues and cells, which was associated with poor clinical prognosis in BC patients. In this experimental study, USP2 depletion resulted in decreased cell proliferation, migration and invasion in BC cells. USP2 stabilized the EZH2 (Enhancer of zeste homolog 2) protein by directly binding to it, thereby reducing its ubiquitination. Ectopic introduction of EZH2 restored cell growth and invasion of BC cells, which had been inhibited by USP2 silencing. USP2-mediated stabilization of EZH2 promoted the enrichment of histone H3K27me3 and repression of SOX1. Involvement of the USP2-EZH2-SOX1 axis in tumor formation was ultimately verified in vivo. These findings revealed that a USP2-EZH2-SOX1 axis orchestrates the interplay between dysregulated USP2 and EZH2-mediated gene epigenetic silencing in BC progression.

Conclusions

Though the natural history and course of BC is well known, no single agent has been categorically proved to be the best for chemoprevention of BC.

One of the important reasons for this caveat could be the poly-factorial aetiology of the disease, significant variation in incidence both geographically and climatically, poor identification and reporting of the disease prevalence and the vast difference in the treatment results based on stage or grade of disease. This probably explains why chemoprevention of BC is a path less trodden.

The understanding of BC epidemiology and risk factors provides an optimal foundation for disease prevention and early initiation of care of affected patients. Exhibiting data on BC incidence, morbidity, and mortality in medical departments and offices could help the treating medical professionals for initiating chemoprevention. It is recommended that pamphlets detailing the contributing factors for the disease should be created and distributed to everyone attending the clinic with suggestions for minor adjustments in the daily routines of susceptible people. Screening is a possible tool to achieve good results for early diagnosis of BC. However, screening programs in BC have been discussed and criticized. Techniques like early detection of microhematuria have been incorporated into practice only regionally. There is also insufficient data available to show that BCs detected earlier would improve survival.

It is pertinent to identify the exact genetic alterations that could predispose the person to BC and adopt chemopreventive measures in the susceptible population. Studies pertaining to various genetic factors influencing bladder carcinogenesis and the role of genetic manipulations in reducing the risk of BC have been on the pipeline and hold promise in future Agents like difluoromethyornithine, which inhibits the enzyme ornithine decarboxylase that contributes to malignant transformation have not stood the test of time as chemopreventive agents.

There is now adequate evidence in literature to suggest the possible role of sex steroid hormone receptors including AR, ER, PR and various other orphan receptors mediated signals in the genesis and progression of BC particularly of the UBC variety. Studies on UBC tissue specimens for AR and ER have clearly demonstrated that excessive or reduced expression of these receptors as well as alterations in their upstream or downstream pathways correlated well with outcomes of this cancer entity. AR activation correlates with promotion of urothelial tumorigenesis and progression. ER α expression is protective against development of UBC, whereas ER β expression gets up-regulated in high grade &/or muscle invasive UBC. It is also interesting to note that there exists an inverse relationship between AR expression and advanced disease, indicating biphasic nature of receptor behavior during the natural course of the disease. Identification of these hormonal factors could enable the clinicians to adopt preventive and therapeutic measures for BC in susceptible populations. Explorative studies are required to identify the potential role of Tamoxifen and 5 alpha reductase enzyme inhibitors in preventing BC.

For the population at large, it is imperative that health and policy interventions should be adopted to promote smoking cessation, reduce airborne pollutants, ensure safe drinking water and reduce exposure to harmful herbs and agents which could effectively decrease exposure to urinary carcinogens causing BC. Lifestyle modifications including avoiding alcohol consumption, quitting smoking, performing regular physical exercise, reducing red meat in food and supplementation of fruits and vegetables rich in vitamin B in the diet coupled with daily consumption of at least 2-3 L of water could be helpful to retard the onset of BC. Etodolac, rofecoxib and aspirin provide a beacon of hope as drugs which might be useful for clinical treatment and prevention of BC in future.

Conflict of Interest:

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