REVIEW ARTICLE

The status of chemoprevention in the current cancer therapeutic armamentarium

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Summary

Cancer mortality nowadays remains unacceptably high despite immense advances in the understanding of the mechanisms of carcinogenesis, in bringing potent new drugs to the clinic and in treating several rare forms of cancer. Many scientists suggest that overall cancer mortality statistics are unlikely to change in a fundamental way until there has been a re-orientation of emphasis in cancer research that will direct greater resources towards prevention of disease development, rather than treatment of end-stage disease. Cancer chemoprevention represents a rather new rational approach in the management of cancer. Although the results of chemoprevention clinical trials will appear in the near future, the current preclinical and initial clinical published data outline the significant future perspective of cancer chemoprevention.

Key words: breast cancer, carcinogenesis, chemoprevention, colorectal cancer, lung cancer

Introduction

The continuing raise of the incidence of malignant neoplasms, such as breast, lung and colorectal carcinomas, combined with the widely accepted “plateau phase” concerning the efficacy of the existing chemotherapy in advanced disease, highlights the intense demand for the development of novel cancer therapeutic and preventive strategies. Although the current advances of basic cancer research and therapeutic development are extraordinary, the mortality rate from malignant neoplasms still remains high [1]. Therefore, reevaluation of the basic principles regarding carcinogenesis as well as the adoption of an alternative approach to cancer prevention and treatment appears inevitable. To date, the major proportion of basic and clinical anticancer research efforts is mainly focused in the treatment of advanced disease. However, this approach cannot be regarded as a rational one, since the advanced stages are characterized by genetic heterogeneity and high tumor burden [2]. Moreover, the misleading definition of cancer as a disease mainly correlated with abnormal cellular proliferation has driven to an overshooting emphasis in the testing and development of cytotoxic drugs that have the capacity of killing the cancer cells [1]. Unfortunately, most of these agents are also toxic for a great number of normal cells and tissues, such as the gastrointestinal tract, heart, bone marrow, lungs, kidneys and central nervous system. The side effects caused to such vital organs might represent the main cause of death in some cancer patients.

An alternative analysis of cancer pathogenesis is the one that approaches cancer as the final stage of a multistep long-term accumulation of genetic and epigenetic aberrations at the molecular level that results in abnormal differentiation of cells and tissues. The process that will eventually produce the infiltrative and metastatic carcinoma is the so-called carcinogenesis [3]. Besides the histological observation, the molecular
mechanisms of this rationale have not been satisfactorily elucidated. For example, several genetic abnormalities have been detected not only in cancer cells, but also in histologically defined premalignant lesions. The malignant transformation of a normal cell is initiated by genetic defects caused by tissue-specific carcinogens. Oncogenes and tumor-suppressor genes are the two main gene groups that are responsible for the proliferation advantage that characterizes cancer cells. As the transformed cell continues to grow and differentiate, more genetic defects are accumulated, for example complete deregulation of apoptosis, while the infiltration of the basic membrane represents one of the main steps in the carcinogenic procedure [4].

Many scientists worldwide suggest that more focus is needed in the evaluation and control of the initial steps of carcinogenesis rather than trying to treat the advanced stages. Cancer chemoprevention represents the rational and practical approach of this thought.

Definition of cancer chemoprevention

Chemoprevention represents a very promising strategy in the global effort of cancer prevention and treatment. Chemoprevention was first defined by Sporn in 1976 as the use of specific natural or synthetic chemical substances that reverse, inhibit or prevent the evolution of precancerous lesions into advanced carcinoma [5]. Chemoprevention should not be confused with chemotherapy. The main aim of chemotherapy is killing cells, particularly cancer cells, in the hope of preventing further cancer progression. Chemoprevention, on the other hand, involves administering nontoxic agents to otherwise healthy individuals who may be in increased risk for cancer development.

Table 1. Proposed mechanisms of action of chemopreventive agents

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have chemopreventive properties [7]. Many proposed mechanisms of action try to enlighten the anticancer action of all these agents, while the rapidly increasing knowledge in molecular oncology has resulted in the expanded research interest in signal transducing pathways with the primary scope being the evaluation and targeting of new critical molecules and events with novel chemopreventive agents [8].

**Development of chemopreventive agents**

A potential chemopreventive agent, like a potential new drug, goes through several phases before it can be administered to large numbers of people. An agent starts with preclinical evaluation and gradually proceeds into clinical trials of various phases [2]. Although most of the candidate chemopreventive agents are natural products, they are usually evaluated in high doses with potential side effects. To date, the immediate and long-term side effects of these agents are largely unknown [9]. Moreover, the results of the so far completed cancer chemoprevention trials are somehow conflicting. A typical example is the debate that aroused from the finding that β-carotene use in smokers was correlated with increased incidence of lung cancer [10,11]. The results of all these clinical trials outline the need for careful and rational design of large-scale cancer chemoprevention trials that could give solid conclusions and influence clinical practice.

(A) **Preclinical evaluation**

Initial *in vitro* experiments used induced carcinogenesis in various tissues in animal models (e.g. colon, breast) [12]. A significant parameter in the evaluation procedure of candidate chemopreventive agents is the existence of “organotropism”. For example, there are natural and synthetic antioxidants that inhibit liver carcinogenesis, while inducing tumor formation or carcinogenesis in other tissues [13]. Improved research protocols are in progress, evaluating candidate chemopreventive agents in a variety of tissues.

When the results of *in vivo* experiments are encouraging, candidate agents are thoroughly tested for efficacy, toxicity and pharmacokinetics. Only the agents proved to have the optimal efficacy/toxicity ratio in animal models will enter the phase of clinical evaluation.

(B) **Early clinical trials**

Candidate chemopreventive agents with promising preclinical results are then evaluated in initial clinical trials that usually involve 25-100 individuals with duration of less than a year in order to define their pharmacokinetics and the dose/toxicity ratio. Regarding agents that are already in use in humans and their pharmacokinetic features are familiar (e.g. vitamin A, β-carotene), phase I clinical trials could be omitted. The same applies for agents that are used by humans for other clinical conditions in doses and duration of administration at least equal with those that are planned to be used in cancer chemoprevention trials [14].

(C) **Phase II clinical trials**

Those are randomized, double-blind, placebo-controlled trials conducted in 100-1,000 healthy individuals or patients in each study arm with 1 to 5-year duration. One of the main aims of these trials is the evaluation and identification of intermediate biological markers – “biomarkers” that will contribute in the future estimation of cancer incidence. Examples of “biomarkers” used in cancer chemoprevention trials are dysplasia and/or intraepithelial neoplasia of the prostate and cervix, dysplastic leukoplakia of the upper aerodigestive tract epithelium, Barrett’s esophagus, colorectal polyps, superficial bladder papillomas, bronchial dysplastic metaplasia and atrophic gastritis [14].

(D) **Phase III clinical trials**

These trials are conducted with a very promising candidate chemopreventive agent with high efficacy/toxicity ratio. They include 1,000-10,000 individuals and their duration is at least 10 years, as their impact in cancer incidence is the primary end-point [15].

**Applications of cancer chemoprevention concept in cancer patients**

Cancer chemoprevention strategy in conjunction with the increasing knowledge regarding the molecular mechanisms of carcinogenesis has resulted in promising clinical results for many solid tumors. The present review summarizes the existing clinical data and highlights the future perspectives of chemoprevention in lung, breast and colorectal cancer that form the vast majority of malignant tumors.

1. **Lung cancer**

   Lung cancer is the major cause of cancer death. Despite intense research and the therapeutic advances
of the last decades, the prognosis of patients with lung cancer remains dismal and only <15% of them will survive 5 years after the initial cancer diagnosis [16]. The poor clinical outcome of these patients is mainly attributed to the lack of effective methods of early diagnosis and suboptimal therapeutic options for advanced-stage disease [17].

Tobacco use is considered the major risk factor of lung cancer carcinogenesis. Therefore, long-term smokers are usually used as the treatment arm in lung cancer chemoprevention trials [18]. The rationale of lung cancer chemoprevention is based in two basic principles of tumor biology, the multi-step nature of carcinogenesis and the concept of field cancerization [19]. This term was first introduced by Slaughter et al. in 1953 in order to describe the variety of histological lesions that can be found in normal-appearing epithelium, nearby a squamous cell carcinoma in the oral cavity and larynx [20]. This term also outlined that the presence of genetic and phenotypic abnormalities in a region is correlated with increased risk of cancer formation in the entire respiratory epithelium and can be used for the identification of high risk individuals. A typical example of the field cancerization concept is the variety of histological abnormalities caused by tobacco in the respiratory epithelium. The widespread presence of precancerous lesions in the respiratory epithelium is in accordance with epidemiological data showing that long-term lung cancer survivors have an increased risk of a second lung cancer [21]. A plethora of genetic and epigenetic phenomena is gradually implicated in respiratory epithelium carcinogenesis [22]. Inhibition of one or more of these preinvasive lesions could significantly prevent cancer growth.

Retinoids represent one of the most important classes of chemopreventive agents that are currently under intense evaluation for the prevention of respiratory epithelium carcinogenesis [23]. Retinoids consist a group of natural and synthetic chemical substances, structurally similar with vitamin A [23]. Until 1987 it was only known that retinoids are implicated in gene transcription control, but the precise mechanism was still a mystery. This was the year that two research groups identified the retinoids’ receptors [24,25]. Many scientists have now concluded that retinoids’ actions in the molecular level are principally modulated through their receptors, but the exact mechanism is still unknown [26]. Two types of retinoid receptors have been identified, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). There are 3 RAR isotypes and 3 RXR iso- types (α, β, and γ), encoded by distinct genes, and for each isotype there are at least 2 isoforms which differ in their N-terminal A regions and are generated by differential usage of promoters and/or alternative splicing. Like other members of the nuclear receptor superfamily, the retinoid receptors act as ligand-activated, DNA-binding, transcription factors through binding as RAR/RXR heterodimers to cis-acting RA response elements present in cognate genes [8]. Epidemiological and experimental data support the possible role of retinoids in the prevention of respiratory epithelium carcinogenesis [19]. The use of retinoids in a wide range of cancer cell cultures has shown their capacity of inducing differentiation and inhibiting cellular proliferation (e.g. epithelial carcinomas, melanomas, neuroblastoma, leukemia), while they can also inhibit carcinogenesis in animal models.

So far, clinical experience with retinoids in skin diseases (e.g. psoriasis) [27,28], in acute promyelocytic leukaemia (the typical example of differentiation therapy in malignant tumors) [29], and the few conducted cancer chemoprevention clinical trials in patients with precancerous and cancerous lesions [30-32] revealed two major caveats. The first problem is their side-effects that might cause treatment termination, while the second problem is the gradually developed resistance during their use.

Several randomized lung cancer chemoprevention trials using retinoids and natural derivatives have been conducted during the last decade with conflicting results. Moreover, a recent randomised phase II study with retinoic acid in long-term smokers revealed that smoking cessation is superior from the absolute benefit of retinoids [33]. Two of the most important conducted lung cancer chemoprevention trials were ATBC and CARET. ATBC included heavy smokers and evaluated the efficacy of β-carotene and toco-pherol use, without significant results [34]. Noteworthy was the finding that β-carotene was correlated with statistically significant increase of lung cancer incidence and mortality. The same results were observed in CARET study [11]. One possible explanation of these disappointing results is that the most important of the retinoid receptors – RAR/β – has been found to be downregulated since the early stages of respiratory epithelium carcinogenesis [35]. Many theories have been proposed for this crucial molecular event, but the most convincing seems to be epigenetic aberrations, such as methylation and acetylation abnormalities [22,36].

In the last 20 years intense effort has been made in order to develop new synthetic retinoids with little progress [37]. Deeper understanding of the retinoids’ role in differentiation, cellular proliferation and apop-
tosis might radically change the developmental process of new chemopreventive agents in a more selective and effective way [26,38].

(2) Breast cancer

Breast cancer is the most frequent malignant tumor in females [39]. Although mammographic early diagnosis has resulted in breast cancer mortality decrease, the prospects of this technique are exhaustible [40]. An alternative approach is cancer chemoprevention. Control of exposure to estrogens represents a significant parameter in breast cancer chemoprevention strategy [41]. Many of the widely known risk factors are correlated with increased or extended estrogen exposure (e.g. early menarche, delayed menopause, delayed first pregnancy) [42]. It has been suggested that estrogen influence is associated with genetic predisposition (e.g. BRCA1/2 gene mutations, Li-Fraumeni syndrome) and other factors, significantly determining breast cancer risk [43].

The results of recently conducted randomized clinical trials have reinforced the status of breast cancer chemoprevention. Tamoxifen and raloxifen are selective estrogen receptor modulators (SERMs) that have revealed significant breast cancer chemopreventive properties in patients with various risk factors [44]. Although their breast effects are similar, they differ in their effect in endometrium [45]. Tamoxifen, but not raloxifen, has been associated with a slight increase of endometrial cancer risk, with the major impact in women older than 50 years old as well as a minor increase of benign endometrial pathologies [46,47].

The first clinical documentation of tamoxifen chemopreventive properties was published 20 years ago and referred to contralateral breast cancer decrease in patients taking this agent [48]. This clinical observation was verified by further clinical trials [49]. The largest tamoxifen chemopreventive clinical trial involved 13,000 high risk women who took the drug for 5 years and the risk of breast cancer growth was calculated [47]. It was proved that tamoxifen significantly decreased breast cancer incidence in the patient group taking the drug, especially in the subset of women with in situ breast carcinoma or atypical hyperplasia. Three more clinical trials have been conducted or are in progress showing again the beneficial effect of tamoxifen regarding estrogen receptor positive breast cancer incidence [50-53]. All these trials also revealed the toxicity profile of tamoxifen. Besides its potential harmful effect in the endometrium, a series of other less frequent side effects were also observed, such as cataract and increased risk of thromboembolic events [44]. Based on these data, a new SERM – raloxifen – was developed and proved to have the same activity with tamoxifen, but less toxicity.

The initial raloxifen trial (MORE) included more than 7,000 menopausal women with osteoporosis and with no other risk factor. Raloxifen was proved to have significant effect regarding breast cancer incidence without most of the tamoxifen side effects [54]. These findings results resulted in the design of more clinical trials. CORE study was the sequel of MORE study as its major end-point is the evaluation of breast cancer risk after a total 8 years of raloxifen use in 60 mg/d dosing. RUTH study is evaluating the effect of the same dose of raloxifen regarding the risk of cardiovascular events and infiltrative breast cancer in menopausal women [55]. Finally, STAR study directly compares raloxifen and tamoxifen effect in menopausal women with high breast cancer risk and its results are awaited with great interest [56].

Retinoids have also been evaluated in breast cancer chemoprevention. Fenretinide is a synthetic product of retinoic acid [57]. Preclinical and clinical data were used in the design of a chemoprevention trial of fenretinide in women with high breast cancer risk, that is in women with a prior history of breast cancer surgery [58,59]. Noteworthy were the results in the premenopausal group of patients, given the very poor clinical outcome and the aggressive biologic behavior of these tumors [60].

Other candidate chemopreventive agents tested in breast cancer chemoprevention trials are the aromatase inhibitors, based on their encouraging results in the treatment of advanced/metastatic breast cancer, in the neoadjuvant setting and the extended adjuvant clinical use [61], and the selective cyclooxygenase-2 inhibitors that seem to have potential synergistic effect with aromatase inhibitors [62].

(3) Colorectal cancer

Colorectal carcinomas are considered the final stage of a series of histological and molecular changes that contribute to the malignant transformation of normal colonic epithelium through the intermediate phase of adenomatous polyps [63]. Molecular analysis of colorectal polyps and carcinomas revealed a multistep carcinogenesis model of gradually accumulated genetic and phenotypic aberrations [64]. Chemoprevention offers the chance of regression or inhibition of adenomatous polyps’ growth, as well as their evolution in carcinomas. Recently published clinical
studies suggest this therapeutic approach in patients with familial adenomatous polyposis (FAP), as well as in healthy individuals with clinical history of sporadic adenomas [62].

The major classes of chemopreventive agents that have been tested in colorectal carcinomas are the following:

(a) Aspirin and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Epidemiological data have shown that aspirin and NSAIDs may reduce the incidence of various neoplasms, among them colorectal carcinomas. There are two isoforms of the cyclooxygenase (COX) enzyme: COX-1 and COX-2, which differ in many respects. Recently, another isoform, COX-3, along with two smaller so-called partial COX-1 proteins were identified [62]. COX-1 and COX-2 are similar enzymes consisting of a long narrow channel with a hairpin bend at the end. Both isoforms are membrane-associated, resulting in the arachidonic acid biochemical chain reactions. Although the catalytic activities and tertiary structures of both isoforms are similar, COX-2 has a broader affinity for substrates. A single amino acid substitution (valine instead of isoleucine) in the NSAID binding side-pocket of COX-2 determines the COX-2 selectivity of designed selective inhibitors. COX-1 is expressed constitutively in most tissues and synthesizes prostaglandins (PGs) that are required for physiologic functions, such as gastrointestinal protection, regulation of renal blood flow and platelet activity. However, a possible role of COX-1 in carcinogenesis cannot be excluded, based on preclinical and clinical evidence. This is mainly sustained by the reported chemopreventive effect of low-dose aspirin, a drug that causes rather selective inhibition of platelet COX-1. COX-2, on the contrary, is not detected in most normal tissues. It is induced by proinflammatory and mitogenic stimuli and enhances the synthesis of PGs in inflamed and neoplastic tissues. It has been found to be frequently overexpressed in a wide variety of precancerous and cancerous lesions [65]. In normal colonic human epithelium, COX-2 generally is downregulated. However, its expression is upregulated by approximately 50% in colorectal adenomas and 85-90% in colorectal cancer [65].

Preclinical and clinical data have provided evidence that selective inhibitors of COX-2 (COXIBs) are safe and effective for the prevention and regression of colonic adenomas [66]. Moreover, several encouraging results that have aroused from preclinical studies have resulted in clinical studies evaluating COXIBs in the treatment of colorectal cancer [62]. Recently, a large clinical trial suggested that celecoxib, a selective COXIB, reduces the number of colon polyps that occurs in patients with FAP and is now considered as an adjunct to usual care of such patients [66]. However, it should be noted that the beneficial effect of celecoxib in FAP was achieved with high doses that might also affect COX-1, due to the reported in vitro low selectivity of this drug. Although celecoxib has been approved for FAP treatment, the fact is that the drug, in the doses used, only reduces the growth of colorectal adenomas, whilst no data is still available on its effect in the reduction of the incidence of colorectal cancer. Additionally, a discrepancy has been observed between population-based observational studies reporting reduction of incidence and death from colorectal cancer with the use of aspirin and nonselective NSAIDs and randomized clinical trials performed with aspirin, sulindac and COXIBs reporting a less profound effect in terms of reduction of the incidence of colorectal adenomas or regression of colorectal polyp number and size [62]. Preliminary clinical results in patients with metastatic colorectal cancer have shown that COXIBs may both add to responses seen with chemotherapy [62], as well as decrease the adverse effects seen with chemotherapy [67], although recently reported results are somewhat conflicting [68].

Ongoing clinical trials investigating COXIBs in colorectal cancer prevention are perhaps the most exciting. Because of important similarities in the biology of FAP and sporadic colorectal cancer, therapeutic strategies that are effective in FAP may also be applicable to patients with sporadic colorectal adenomas. The results of these clinical trials could create a tremendous long-term effect on colorectal cancer incidence and mortality.

(b) Folate

Accumulating evidence suggests that increased consumption of fruits and vegetables might reduce colorectal cancer risk [69]. Folate is a micronutrient that exists in high quantities in fruits and vegetables. Epidemiological data have shown reduced incidence of colorectal carcinomas among people with high folate intake [63]. The correlation of diet folate intake and cancer risk is altered with alcohol consumption as well as with other agents that interfere with folate metabolism, such as methionine and some vitamins [70]. Folate and its metabolites play a crucial role in DNA construction and methylation processes. To date 3 mechanisms have been proposed to explain
this beneficial correlation: modulation of DNA methylation, deregulation of DNA precursor equilibrium, and chromatin changes [71]. However, the optimal folate dosing regarding safety and efficacy has not been defined yet.

(c) Calcium and Vitamin D

Diets rich in animal fat and red meat have been epidemiologically associated with increased risk of colorectal adenomas and carcinomas [72,73]. Although the exact mechanism is still unclear, it has been speculated that those diets might increase the production of secondary cholic acids that either result in enhanced proliferation of colonic epithelium or induce tumorigenesis as it has been shown in animal models [74]. Calcium intake might reduce the incidence of colorectal cancer due to direct linkage with cholic acids into the colonic lumen [75] or due to direct inhibition of cellular proliferation of the epithelial cells of the colonic mucosa [71]. Large-scale randomized clinical trials in patients with colorectal adenomas have revealed that calcium intake is correlated with a moderate but statistically significant decrease of the colonic adenomas relapse risk [76], although there are also studies without the same promising results [77].

The role of calcium in colorectal carcinogenesis is directly linked with vitamin D, since its active metabolite –1,25(OH)2D3 – participates in the colonic calcium intake. Moreover, vitamin D has a pivotal role in a plethora of biologic interplays, through its nuclear receptors that are members of the nuclear receptor superfamily [8]. In vitro studies have shown that vitamin D3 and calcium can inhibit cellular proliferation, induce differentiation and enhance apoptosis [78]. Recently published randomized clinical trials revealed the synergistic action of calcium and vitamin D regarding colon cancer prevention [79].

In conclusion, based on the data acquired so far, it can be assumed that calcium and vitamin D intake can reduce the colorectal cancer risk. However, there are still many undefined issues, such as dosing schedule and possible long-term toxicity [80].

(d) Hormone replacement treatment (HRT)

Many trials have studied the association of HRT, especially estrogens, and colorectal cancer incidence [81]. To date it seems that HRT significantly reduces colorectal cancer mortality, its beneficial effect duration is for at least 5 years, while colorectal carcinomas diagnosed in women taking HRT are in more advanced stages. The influence of HRT regarding adenomas formation has also been extensively studied [82-84]. Although the existing data remain conflicting, it seems that HRT might have protective role regarding the formation of large adenomas (>1 cm), and reduces the relapse risk in women aged >60 years with distal adenomas. The beneficial effect of estrogens in colorectal carcinogenesis might be attributed to the reduction of secondary cholic acids production, to downregulation of growth factors, to direct effect on the epithelial cells of the colonic mucosa, to insulin changes or combination of all these mechanisms [85]. Regarding hyperglycemia and hyperinsulinemia, it has been assumed that they represent independent risk factors of colorectal carcinogenesis [86]. The aforementioned data suggest that estrogens, in contrast with the other referenced factors, act in the later stages of colorectal carcinogenesis.

(e) Vitamins, Antioxidants, Fibers

Besides the high folate content, it has been suggested that the beneficial role of diets rich in fruits and vegetables regarding colorectal cancer risk can also be attributed to vitamins with antioxidant properties and fibers [87]. To date, clinical data from large-scale randomized trials and smaller cohort studies do not suggest a protective effect of diet supplements with β-carotene and vitamins A, C, D, and E in the prevention of colorectal cancer [63,88]. Similar results emerged regarding the use of diet fibers and colorectal cancer incidence, as well as the prevention of adenomas formation [89].

Future perspectives of cancer chemoprevention

The new era of genomics, proteomics and their applications offer new insights in the deeper understanding of the carcinogenetic process. Basic and translational research using new findings and technologies will contribute to the identification of novel molecular and genetic biomarkers that will be used for the prediction of future cancer risk, enabling patient stratification in large-scale cancer chemoprevention studies. Moreover, new molecular predictive markers might emerge for the newly designed chemopreventive agents.

To date, the existing evidence does not justify the wide use of chemopreventive agents. The major reasons are: (a) The need of large-scale prospective randomized clinical trials that are difficult to conduct due to the large amount of money needed; (b) the pharmaceutical industry does not significantly con-
tribute to the design and implementation of such trials due to the long-term expected potential clinical benefit; (c) the study groups of such trials are consisted of healthy volunteers or individuals with high cancer risk.

Another important issue is the development of novel chemopreventive agents with innovative mechanisms of action. The existing agents have documented chemopreventive action through preclinical and clinical data, but they do not represent the optimal choice for widespread use because of inadequate efficacy and unacceptable toxicity.

Cancer chemoprevention is not a simple matter and conclusions over its impact on carcinogenesis require long periods of observation. Nevertheless, it might constitute a major future weapon in the effort of reducing cancer incidence in individuals with high risk of getting cancer.

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