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FRONTIER

Bisphosphonates as potential adjuvants for patients with cancers of the digestive system

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Abstract

Best known for their anti-resorptive activity in bone, bisphosphonates (BPs) have generated interest as potential antineoplastic agents given their pleiotropic biological effects which include antiproliferative, antiangiogenic and immune-modulating properties. Clinical studies in multiple malignancies suggest that BPs may be active in the prevention or treatment of cancer. Digestive tract malignancies represent a large and heterogeneous disease group, and the activity of BPs in these cancers has not been extensively studied. Recent data showing that some BPs inhibit human epidermal growth factor receptor (HER) signaling highlight a potential therapeutic opportunity in digestive cancers, many of which have alterations in the HER axis. Herein, we review the available evidence providing a rationale for the repurposing of BPs as a therapeutic adjunct in the treatment of digestive malignancies, especially in HER-driven subgroups.

Key words: Bisphosphonates; Cancer; Gastrointestinal; Hepatobiliary; Human epidermal growth factor

Core tip: Bisphosphonates demonstrate antineoplastic activity in various malignancies but have received little attention in cancers of the digestive tract. We review the preclinical and clinical experience with bisphosphonates in digestive cancers and discuss their potential therapeutic application in this disease group, particularly in the context of recent data on bisphosphonate-induced inhibition of human epidermal growth factor receptor signaling.

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INTRODUCTION

Cancers of the digestive system, including esophagogastric, hepatocellular, pancreatobiliary, small and large bowel carcinomas were projected to comprise about 17% of the 1.6 million new cancer diagnoses made in the United States during 2014[1]. Systemic therapy with cytotoxic chemotherapy and/or molecularly targeted agents is the mainstay of treatment for these cancers when they are at an advanced stage. Despite advances in drug development and improved insights into the molecular pathobiology of these diseases, median survival for most stage Ⅳ digestive cancers is less than 12 mo, the exceptions being small bowel and colorectal adenocarcinoma. These sobering facts underscore the chasm between theoretical knowledge and clinical application, and highlight the urgent need for novel therapeutic approaches.

In recent years, there has been a growing recognition that some drugs that are effective in treating one type of disease can be "repurposed" for treatment of an unrelated condition. Repurposing is a particularly attractive option because the therapeutic agents have known safety profiles.

Bisphosphonates (BPs) inhibit osteoclast-induced bone resorption which is a property that underlies their use in the treatment of bone resorption disorders such as osteoporosis and Paget's disease. In patients with advanced cancer, BPs are used in the supportive management of complications such as hypercalcemia of malignancy, and the prevention of skeletal-related complications in patients with bone metastases. Indications that BPs might have direct antineoplastic effects came from randomized clinical trials of adjuvant estrogen suppression therapy in women with resected breast cancer which revealed that the addition of BPs not only decreased bone density loss but also decreased the risk of contralateral breast cancer and improved disease-free survival[2-4]. The beneficial effects of BPs on clinical outcomes were most pronounced in postmenopausal women in whom systemic estrogen levels are low[4]. Subsequent randomized trials in patients with multiple myeloma and other advanced solid tumors such as lung and prostate cancer provided additional evidence that BPs improve oncologic outcomes including overall survival and prevention of bone metastases[5-10]. In addition, a number of observational studies have reported decreases in risk of breast and colorectal cancer among BP users[11-17]. Collectively, these data suggest that BPs may be clinically active in the prevention as well as treatment of cancer. Studies focusing on the activity of BPs in patients with digestive tract cancers are limited, however.

BPs, especially nitrogen-containing bisphosphonates (NBPs), have antiproliferative, antimotility, pro-apoptotic, antiangiogenic and immunomodulatory properties[5,18,19]. Many of these activities are attributed to inhibition of the mevalonate synthesis pathway by NBPs[20,21]. Recently, NBPs have been shown to bind to and inhibit signaling by the human epidermal growth factor receptor (human EGFR/HER), causing apoptosis in HER-driven cancer cell lines and synergizing with HER tyrosine kinase inhibitors[22,23]. Many digestive cancers have alterations in the HER axis, highlighting an actionable target for NBPs. In this review, we summarize the preclinical and clinical experience with BPs in digestive malignancies and discuss how BPs might be integrated into current treatment strategies.

BISPHOSPHONATE STRUCTURE, FUNCTION AND MECHANISM OF ACTION

BPs are inorganic pyrophosphate derivatives with a central nonhydrolyzable carbon atom, a hydroxyl group, and two flanking phosphate groups (Figure 1). The chemical structure of BPs confers a strong affinity for the mineral component of bone, which facilitates their uptake by osteoclasts[24]. Bone resorption is inhibited by BPs due to osteoclast growth arrest and apoptosis. The addition of a nitrogen group increases the antiresorptive potency of BPs by up to 10000 fold[21,24]. NBPs currently used in clinical practice include the oral agents alendronate, ibandronate and risedronate, and intravenous formulations such as pamidronate and zoledronic acid (ZA).

The molecular mechanisms of action differ between BPs and NBPs. Early generation BPs, such as etidronate and clodronate, induce osteoclast death by generating cytotoxic ATP analogs, which impair mitochondrial oxygen consumption[25]. As previously mentioned, many of the biological effects of NBPs are attributed to their interactions with the mevalonate synthesis pathway. Among the key components of this pathway are farnesyl pyrophosphate synthase and geranylgeranyl pyrophosphate synthase, which mediate the posttranslational prenylation and activation of small signaling GTPases (*e.g.*, Rab, Rac, Rho, Rap1A and Ras), promoting cell growth, proliferation, migration and survival (Figure 1)[18-21,26,27]. Suppression of the mevalonate synthesis pathway inhibits protein prenylation, arresting these processes in osteoclasts as well as other cell types. In breast cancer cells, ZA inhibits farnesylation of centromere protein-F, preventing assembly of the mitotic spindle apparatus and halting cell cycle progression. The addition of farnesol reverses this process, allowing mitosis to resume[28]. Interestingly, dendritic cells treated with

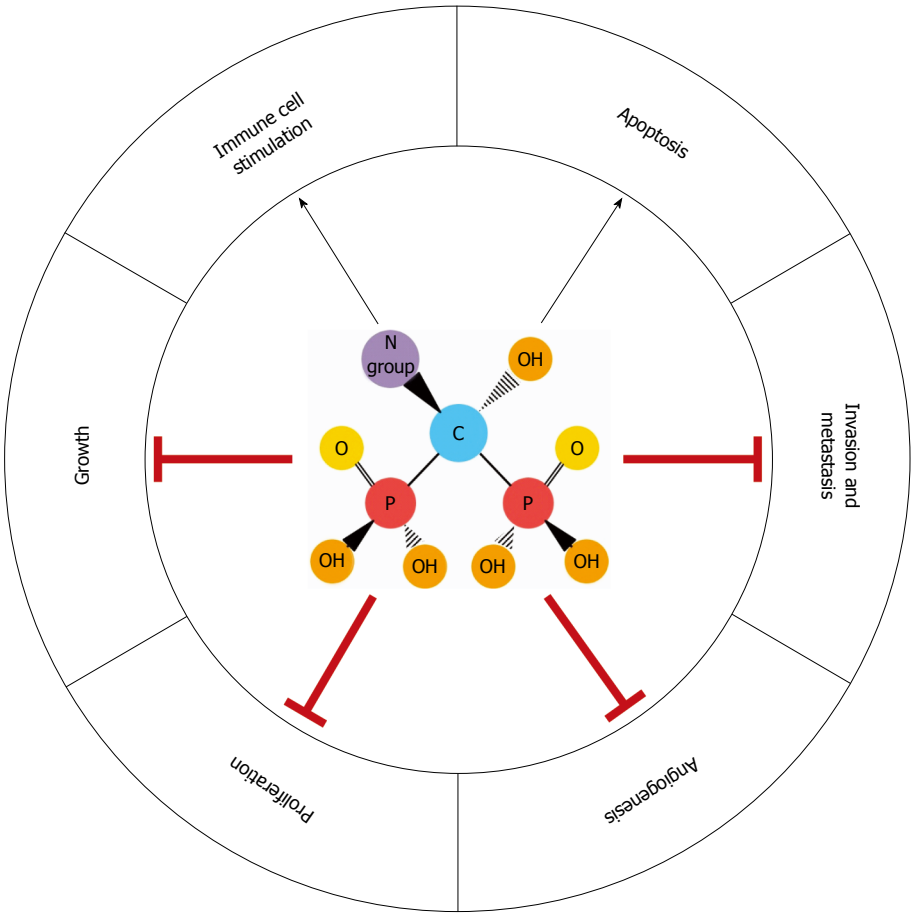

Figure 1 Chemical structure of nitrogen-containing bisphosphonates and effects on the mevalonate synthesis pathway.

ZA have an enhanced ability to stimulate expansion of γδ T cells, which are cytotoxic against a variety of solid tumor cell lines[29,30]. These events are associated with the accumulation of isopentenyl pyrophosphate, a potent chemoattractant and stimulator of γδ T cells. Increased isopentenyl pyrophosphate also promotes formation of cytotoxic ATP analogs, which disable mitochondrial adenine nuclear translocase, causing apoptosis[31]. Furthermore, tumor cells treated with NBPs show increased sensitivity to γδ T cell-mediated cytotoxicity[32]. BPs also target angiogenesis and cell invasion by countering hypoxia-inducible factor-1α, vascular endothelial growth factor, tumor associated macrophages (TAMs) and matrix metalloproteinases[33-35]. These findings illustrate the pleiotropic effects of BPs on cancer cells and the tumor microenvironment (Figure 2).

A novel mechanism of action of NBPs involving the HER pathway has recently been described. Using protein thermal shift, cell-free kinase assays and computational modeling, NBPs have been shown to bind to the tyrosine kinase domain of HER1/2. Binding leads to global inhibition of HER signaling and decreased viability of HER-driven breast and lung cancer cell lines[22]. The growth inhibitory effects persist despite knockdown of farnesyl pyrophosphate synthase, but are completely abrogated by knockdown of HER, indicating that they are dependent on HER and not the mevalonate synthesis pathway. ZA enhances the antineoplastic efficacy of HER1 tyrosine kinase inhibitor, erlotinib, in lung cancer cells, and inhibits tumor growth and viability in cells that have become erlotinib-resistant[23]. These findings highlight the therapeutic potential of co-targeting HER with both NBPs and anti-HER agents, particularly in patients with HER-driven cancers.

It is important to note the unique toxicities of BPs stemming from their mechanism of action. Osteonecrosis of the jaw is one of the most serious side effects BPs, with a reported incidence ranging from 0.85%-18.6%[36]. The use of BPs for malignant *vs* benign indications, intravenous *vs* oral BP formulations, prolonged duration and high cumulative dose of therapy, recent dental procedure, and concurrent therapy (*e.g.*, glucocorticoids, anti-angiogenic agents) are variables that may increase the risk of developing osteonecrosis of the jaw. Atypical femoral fractures are another unusual side effect of BPs, the reported incidence ranging from 0.3 to 11 per 100000 person years[37]. Patients with a prior history of low-energy fracture, glucocorticoid exposure, long duration of BP therapy, pre-existing rheumatoid arthritis or collagen disease and low serum vitamin D levels may be at higher risk. Other

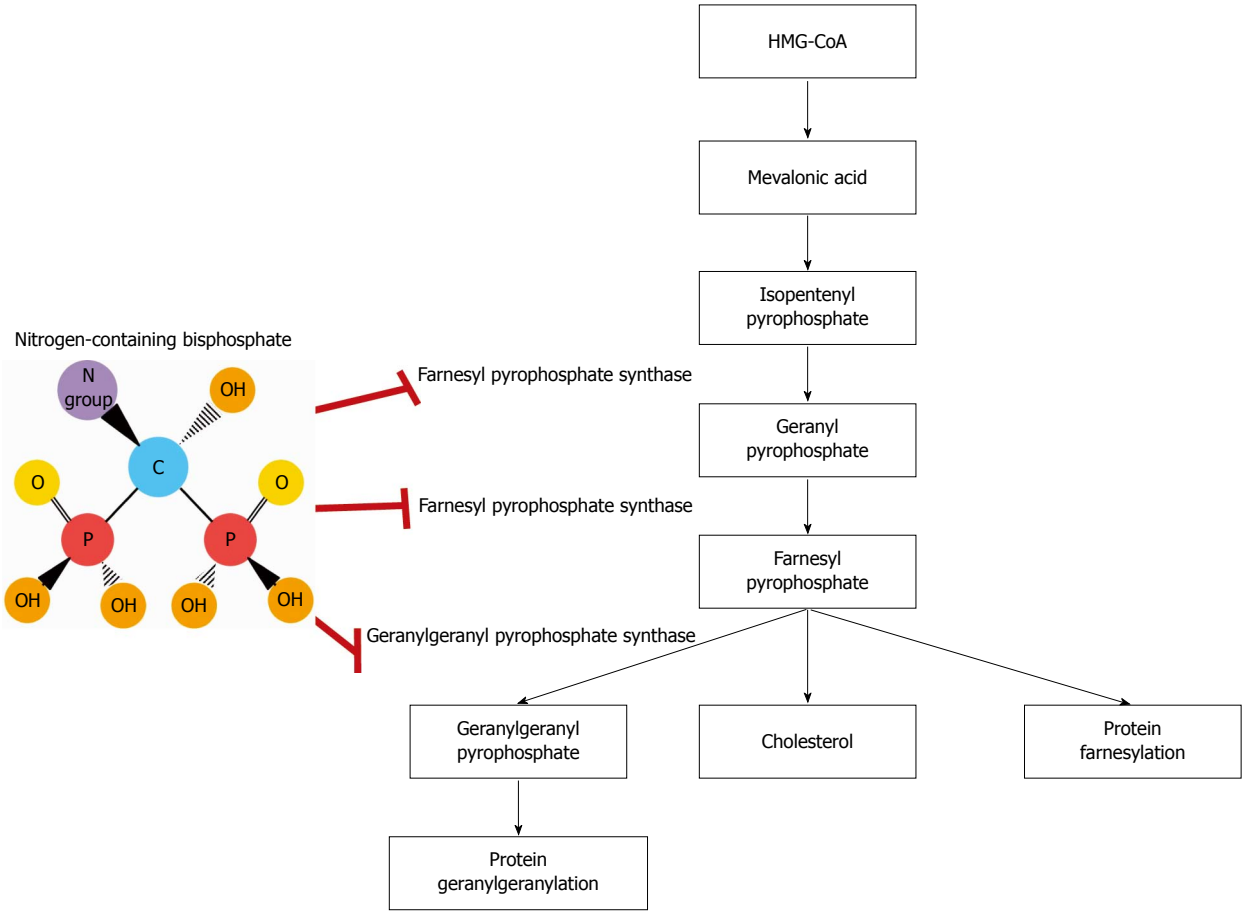

Figure 2 Pleiotropic biological effects of bisphosphonates.

reported adverse events include nephrotoxicity, flu-like symptoms, ocular inflammation, atrial fibrillation and hypocalcemia[38].

BISPHOSPHONATES IN DIGESTIVE CANCERS

Esophagogastric cancers

Studies assessing activity of BPs in esophagogastric cancers are in early stages, but have yielded promising results. *In vitro* chemosensitivity testing performed on the bone marrow aspirate of a patient with metastatic signet ring gastric adenocarcinoma demonstrated synergy with the combination of gemcitabine, oxaliplatin and ZA[39]. The patient was treated with this combination and experienced a durable complete response that included clearance of cancer cells from the bone marrow. In another study, an alendronate-fluoropyrimidine conjugate showed cytostatic activity in gastric adenocarcinoma cell lines[40]. In esophageal squamous cell carcinoma, high centromere protein F expression has been associated with decreased survival, but confers an increased sensitivity to the combination of ZA and cisplatin[41]. In cells that overexpress centromere protein F, the antiproliferative activity of ZA and cisplatin is *synergistic* whereas it is *additive* in cells with low centromere protein F levels. In another study, a synthetic BP analog induced cell cycle arrest, apoptosis and inhibited growth of well, moderate and poorly-differentiated human gastric cancer cell lines *in vitro*, and in a mouse xenograft model[42]. The induction of apoptosis appeared to be linked to activation of ERK1/2, though activation of MEK and Raf-1 was also observed (Table 1).

HER-2 overexpression in 15%-20% of gastric and gastroesophageal junction adenocarcinomas highlights a patient subgroup who might be particularly responsive to the antineoplastic effects of BPs. Patients with HER-2-positive disease experience improved response rates and survival outcomes with the addition of the anti-HER-2 antibody, trastuzumab, to chemotherapy with 5-fluorouracil and cisplatin[43]. In light of recent data showing that NBPs bind to and inhibit HER1/2 signaling[22], there is rationale for evaluating combination therapy with ZA, trastuzumab and chemotherapy in HER-2-positive gastric and gastroesophageal junction adenocarcinomas. There are, however, currently no trials assessing the combination of BPs and trastuzumab in these cancers. The only clinical study evaluating BPs in gastroesophageal cancers is a phase I trial of ZA, IL-2 and IMAB 362 in patients with Claudin-18.2-expressing cancers (PILOT

Table 1 Summary of selected clinical studies of bisphosphonates in digestive cancers

Study Design	Cancer type	Population	Therapy	Main Findings
Prospective studies				
Phase Ⅰ pilot (NCT01671774)	Esophagus, gastric	Advanced disease Claudin 18.2 expression+	IMAB362 + ZA +/- IL-2	Ongoing
Phase Ⅰ	Pancreas	*n* = 23 with resectable disease	ZA once pre-op, and twice post-op	Median/1 yr/2 yr OS: 18 mo/86%/33% Median/1 yr/2 yr PFS: 12 mo/27%/9% No improvement
Phase Ⅱ (NCT01259193)	HCC	Advanced disease	Sorafenib + ZA	Ongoing
Observational studies				
Restricted open cohort study[15]	Colorectal	Region: Denmark 30505 postmenopausal female BP users matched 1:4 BP non-users	Alendronate	Alendronate associated with decreased incidence (HR = 0.69, 95%CI: 0.6-0.79), risk of death (HR = 0.62, 95%CI: 0.52-0.72) and longer survival (HR = 0.82, 95%CI: 0.7-0.97, $P < 0.05$)[1]
Systematic review and meta-analysis[16]	Colorectal	Country: various 20001 cancer cases 392106 patients total	Alendronate, pamidronate, etidronate, ibandronate, risedronate, ZA	Significant decrease in cancer incidence (HR = 0.83, 95%CI: 0.76-0.90)
Case control[17]	Colorectal	Country: Israel Postmenopausal women 933 cancer cases matched 1:1 with controls without cancer	Any oral BP (95% alendronate)	BP use > 1 yr associated with significant decrease in cancer risk (RR = 0.5, 95%CI:I 0.35-0.71)[2]
Case control[46]	Esophagus, gastric	Country: United Kingdom 8636 cancer cases matched 1:4 with controls without cancer	Any BP except pamidronate and ibandronate	Esophagus cancer risk significantly higher in female BP users than non-users (OR = 1.43, 95%CI: 1.18-1.72)[3] Higher risk with alendronate No difference in gastric cancer risk
Nested case control[47]	Esophagus, gastric, colorectal	Country: United Kingdom 15613 cancer cases matched 1:5 with controls without cancer	Any oral BP	Rx for BP associated with significant increase in risk of esophagus (RR = 1.3, 95%CI: 1.02-1.66, $P = 0.02$) but not gastric or colorectal cancer4
Matched cohort[48]	Esophagus, gastric	Country: Denmark History of fracture 13678 cases who filled BP Rx matched 1:2 with controls who did not fill BP Rx	Any oral BP (alendronate > etidronate > ibandronate, risedronate, clodronate)	Highest risk: ⩾ 10 Rx, ⩾ 3 yr 85 cancer cases total BP use associated with significantly decreased risk of esophagus cancer (HR = 0.35, 95%CI: 0.14-0.85, $P = 0.02$)[5] No effect on gastric cancer risk
Matched cohort[49]	Esophagus, gastric	Country: United Kingdom 41826 cases Rx BP matched 1:1 with controls not Rx BP	Any oral BP	207 cancer cases total No increase in risk of esophagus or gastric cancer. Risk not affected by NBP *vs* non-NBP, duration of use, history of GERD[6]
Nested matched case control[50]	Esophagus	Country: United States History of Barrett's esophagus 116 with cancer matched 1:6 with controls without cancer	Etidronate, tiludronate, alendronate, ibandronate, risedronate	< 2% of cases and controls filled Rx for BP Non-significant association between BP use and esophagus cancer risk (incidence density ratio 0.92, 95%CI: 0.21-4.15)[7]
Nested case control using 2 datasets[51]	Esophagus, gastric, colorectal	Country: United Kingdom 55952 cancer cases matched 1:5 with controls without cancer	Alendronate, etidronate, ibandronate, risedronate	BP use not associated with risk of esophagus or colorectal cancer Short but not long term alendronate associated with increased risk of gastric cancer (OR = 1.91, 95%CI: 1.34-2.72, $P < 0.001$) in one dataset[8]
Case control[52]	Esophagus	Country: Taiwan 16204 cancer cases matched 1:4 with controls without cancer	Alendronate, risedronate, clodronate, etidronate	No relationship between BP use and esophagus cancer risk Inverse relationship between esophagus cancer risk and BP duration and frequency of use
Meta-analysis observational data[53]	Esophagus	Country: various 3778 cancer cases 173612 BP users 483797 BP non-users	Ibandronate, etidronate, clodronate, zoledronate, pamidronate, alendronate	No association between BP use and esophagus cancer risk

Cohort study[55]	Esophagus, gastric	Country: United States 1.64 million patients > 68 yr old with history of osteoporosis and/or BP use 2308 cancer cases 624840 BP users	Any oral BP	No association between BP use and esophagogastric cancer risk[9]
Meta-analysis of observational data[56]	Esophagus, gastric, colorectal	Country: various 16662 cancer cases 79379 controls without cancer	Any oral BP	No significant association between BP use and overall digestive cancer risk
Meta-analysis of observational data[61]	Colorectal	Country: various 63363 cancer cases 200047 BP users 1038526 BP non-users	Any oral BP	No significant change or borderline significant decrease in risk of colorectal cancer
Case series[70]	HCC	Country: Italy *n* = 15 patients with bone metastases, heavily pre-treated	ZA	Decreased pain score and analgesic requirements Median OS 10 mo
Retrospective cohort study[73]	HCC	Country: Japan *n* = 31 patients with bone metastases treated with radiation, 12 also received ZA	ZA	Significant decrease in 6-mo time to pain progression of radiated (0% *vs* 34%, *P* = 0.045) and non-irradiated (20% *vs* 66%, *P* = 0.005) bone metastases Significant decrease in 3-mo radiographic progression rate of non-irradiated bone metastases (29% *vs* 91%, *P* = 0.009)

[1]Adjusted for age, colon cancer risk factors, hormone replacement therapy (HRT), non-steroidal anti-inflammatory drugs (NSAIDs)/prednisolone/acetylsalicylic acid (ASA) use in the past 12 mo; [2]Controlled for alcohol consumption, body mass index; [3]Adjusted for smoking, alcohol intake, dyspepsia, proton pump inhibitor (PPI) use, BMI, H. pylori status; [4]Adjusted for smoking status, alcohol intake, BMI; [5]Adjusted for Charlson index, concomitant medications; [6]Adjusted for smoking, alcohol consumption, BMI, use of HRT/NSAIDs/PPI/H2-receptor antagonists, history of Barrett's esophagus, gastroesophageal reflux disease (GERD); [7]Adjusted for race, noncancer disease comorbidity index, use of PPI/NSAIDsPPI, H2-receptor antagonist; [8]Adjusted for BMI, smoking status, alcohol consumption, ethnicity, history of osteoporosis, use of systemic corticosteroids, acid suppressive therapy, anti-inflammatory drugs, vitamin D use, comorbidities (rheumatoid arthritis, diabetes), gastrointestinal disease; [9]Adjusted for age, gender, race, Medicare Part D low-income subsidy, comorbidities (Barrett's esophagus, gastroesophageal disease, alcohol abuse, smoking status and/or chronic obstructive pulmonary disease, obesity, acid-suppressive therapy, bone density testing, diagnosis of fragility fracture, receipt of institutional care, NSAID use. OS: Overall survival; PFS: Progression-free survival; ZA: Zoledronic acid; HCC: Hepatocellular carcinoma.

trial; NCT01671774).

The potential benefits need to be balanced against potential risks, keeping in mind that BP use in patients with a diagnosis of advanced esophagogastric cancers might be of relatively short duration so side effects could be less of a limitation. Severe esophagitis has been reported in users of oral BPs, especially alendronate[44]. Decreasing the dosing frequency of oral BPs, and use of intravenous BPs like ZA which do not come into direct contact the esophageal mucosa have helped to decrease the incidence of esophagitis[38]. Concerns of a potential carcinogenic effect of BPs were raised with reports of esophageal cancer among relatively short-term users (median duration of exposure 1-2 years) of oral BPs[45]. Results of several population-based studies evaluating esophageal cancer risk among BP users and non-users have been inconsistent. Some studies have reported a significantly increased risk among female and long term users of BPs[46,47], while others have reported a decreased risk[48] or no increase in the risk of esophageal cancer among BP users compared to non-users, including those with a history of Barrett's esophagus[49-53]. At this time, the FDA has not concluded that oral BPs increase the risk of esophageal cancer, nor does it endorse endoscopic screening of patients taking oral BPs who do not have symptoms of esophagitis[54]. Concerning the risk of gastric cancer, studies have reported either a decreased risk or no association with oral BP use[46,47,50,53,55,56]. Additional studies are needed to clarify the risk/benefit ratio.

Colorectal carcinoma

NBPs may exert a protective effect on intestinal mucosa. Several observational population-based studies have reported a decreased incidence of colorectal cancer as well as increased post-cancer-diagnosis survival among long-term users of oral NBPs[15-17,57]. Mechanisms underlying the chemoprotective properties of NBPs on the intestine have not been well defined, but direct effects on intestinal epithelial cells as well as the stromal compartment are considered likely possibilities. Macrophage activation by intestinal commensal bacteria can precipitate intestinal epithelial inflammation, genetic abnormalities and malignant transformation. Administration of encapsulated liposomal clodronate was shown to deplete colonic macrophages, inhibit inflammation, Wnt/β-catenin signaling and carcinogenesis in IL-10 knockout mice colonized with *Enterococcus faecalis*[58].

NBPs demonstrate antineoplastic activity in colorectal cancer. ZA induces apoptosis and decreases growth of colon cancer cells *in vitro*[59]. ZA also promotes colon cancer cell death through adoptive immunotherapy. Colon cancer stem cells exposed to ZA demonstrate an enhanced capacity to expand and activate s Vγ9Vδ2 T cells and are, in turn, rendered more susceptible to cytolysis by Vγ9Vδ2 T cells[60].

Upregulation of the HER pathway is pathogenic in

colorectal cancer. Anti-HER1 monoclonal antibodies cetuximab and panitumumab are useful in the treatment of patients with metastatic colorectal cancer whose tumors lack activating *KRAS* mutations. Growth of HER-driven colon cancer cells, but not cells with low EGFR expression, is inhibited by NBPs[22]. Since *KRAS*-mutated colorectal cancers are resistant to the antineoplastic effects of anti-HER1 antibodies, it would be interesting to test whether NBPs sensitize tumors to these agents via dual inhibition of HER and *RAS*.

Despite the strong preclinical rationale and beneficial effects reported by observational studies, composite data from 6 cohort and 4 case-control studies suggest the preventive effect of BPs on the risk of colorectal cancer, if any, is small[61]. Prospective studies are clearly needed to determine the effect of BPs on colorectal cancer outcomes. While it is unlikely that a randomized study of BPs as chemoprevention will be performed, the utility of BPs as adjuncts to standard therapy in patients diagnosed with colorectal cancer warrants investigation. There are no ongoing clinical trials of BPs in colorectal carcinoma currently posted on ClinicalTrials.gov.

Pancreas carcinoma

Activating mutations in *RAS* and HER overexpression are among the most common molecular alterations in pancreas cancer and are actionable targets for NBPs. ZA-induced inhibition of *RAS* and its dependent downstream signal transduction cascades prevents migration and causes growth suppression and apoptosis of human pancreatic cancer cells *in vitro*[62,63]. Erlotinib is FDA approved for metastatic pancreas cancer in combination with gemcitabine based on a phase Ⅲ trial demonstrating a statistically significant, though clinically modest increase (6.24 mo *vs* 5.91 mo, HR = 0.82, *P* = 0.038) in overall survival compared to gemcitabine alone[64]. Low doses of gemcitabine and ZA demonstrate synergy in inhibiting pancreatic cancer cell growth, invasion and metastases *in vitro* and *in vivo*[65]. Given the enhanced antiproliferative activity observed with the addition of ZA to erlotinib[23], it would be interesting to assess the effects of combining chemotherapy with *RAS* inhibition and dual HER inhibition using ZA and erlotinib in advanced pancreas cancer.

BPs promote pancreatic cancer cell death through other mechanisms. Pancreatic cancer cells cultured in ZA are significantly more susceptible to γδ T cell cytotoxicity than non-cultured cells[63]. BPs may also improve the radiosensitivity of pancreas cancer. Genes involved in cholesterol synthesis, including farnesyl diphosphate synthase have been implicated in pancreatic cancer radioresistance[66]. Inhibition of farnesyl disphosphate synthase by ZA was shown to radiosensitize pancreatic cancer cells *in vitro* and *in vivo* in an allograft mouse model.

In addition to their direct effects on tumor cells, BPs may also act upon the stromal compartment in pancreas cancer. TAMs and myeloid derived suppressor cells promote pancreas cancer cell progression by secreting growth factors and impairing host adaptive immune response. In murine pancreatic cancer models, BPs diminish both of these macrophage populations, causing decreases in tumor growth and neoangiogenesis, increased T cell recruitment and improved survival[67,68].

Results of a phase Ⅰ clinical trial of perioperative ZA in patients with resectable pancreas cancer were recently reported[69]. Treatment with ZA was safe but did not significantly improve overall survival compared to historical institutional data (18 mo *vs* 17.7 mo, *P* = 0.9404), and there was no decrease in granulocyte-myeloid-derived suppressor cells in peripheral blood or bone marrow as had been observed *in vitro*[69]. Potential explanations for the absence of an observed benefit include small sample size (*n* = 23) and heterogeneity in the use of adjuvant chemotherapy and/or radiotherapy following surgery.

Hepatocellular carcinoma

Several case reports and small single institutional series have reported improvements in symptoms and disease control among hepatocellular carcinoma (HCC) patients treated with NBPs[70-74]. Benefits include alleviation of pain and hypercalcemia from bone metastases and improved survival. A patient with HCC and bone metastases experienced a durable complete response with the combination of ZA and sorafenib that persisted for 12 mo after treatment discontinuation[71]. In hepatoma cells BPs activate pro-apoptotic cascades, induce cell cycle arrest and inhibit signaling pathways responsible cell proliferation, survival, adhesion, motility and differentiation[75-79]. ZA also suppresses HCC progression through its effects on several immune cell populations. TAMs enable angiogenesis and are associated with increased tumor microvessel density and disease recurrence after surgery or radiofrequency ablation in HCC[80,81]. Treatment with sorafenib strongly induces peripheral blood recruitment and tumor infiltration by TAMs, and suppresses IL-12b, which stimulates natural killer cells. The addition of ZA restores IL-12b levels and depletes TAMs, causing tumor shrinkage, decreased angiogenesis and lung metastases in HCC mouse models[82,83]. ZA-induced amplification of cytotoxic γδ T cells also enhances hepatoma cell lysis[84,85]. These observations suggest that ZA can enhance the activity of sorafenib or rescue sorafenib-resistant HCC.

The human EGFR pathway has been implicated in the progression of liver fibrosis to cirrhosis and hepatocarcinogenesis[86]. Increased EGF expression is part of a 186-gene signature associated with an increased risk of recurrence and poor survival following resection[87]. In mouse and rat models with chemically or surgically induced liver injury, erlotinib

decreased and even reversed fibrosis in some animals, inhibited hepatic stellate cell activation, and prevented hepatocarcinogenesis[86]. These physiological changes were associated with upregulation and downregulation of good and poor-prognosis genes, respectively, thus reversing the poor risk gene signature. A study of erlotinib for the chemoprevention of HCC is currently underway (NCT02273362). Given the inhibitory effects of ZA on HER, it would be interesting to assess combination therapy with erlotinib and ZA in primary as well as secondary prevention of HCC. A phase Ⅱ clinical trial of sorafenib and ZA for advanced HCC was initiated in 2010 (NCT01259193), but results have not been reported yet.

Other digestive malignancies

There are no data, preclinical or clinical, on the activity of BPs in small bowel cancers, likely owing to the rarity of this disease. Next-generation sequencing has identified alterations in ERBB2/HER2 in 15%-30% of duodenal adenocarcinomas[88,89], providing a basis for assessing HER-2-targeted therapies with or without BPs.

In vitro studies in cholangiocarcinomas have shown that ZA causes cell cycle arrest and decreases tumor colony formation, but does not cause apoptosis[90]. The combination of ZA with ABT-737, a BH3 mimetic that sequesters pro-survival BCL-2 proteins, is synergistic in causing apoptosis in cholangiocarcinoma cell lines[91]. The microenvironment of cholangiocarcinomas contains an active immune cell infiltrate that includes TAMs[92], which may be targeted by NBPs to induce tumor cell death and prevent disease dissemination.

CONCLUSION

Bisphosphonates have pleiotropic biologic effects on cancer cells and their microenvironment, providing a rationale for evaluating their use as therapeutic adjuncts in the management, and possibly prevention, of cancer. Mechanistically, BPs target key processes that are universally operational in oncogenesis, maintenance and progression, suggesting their utility across a broad array of malignancies. Though the reported experience on the clinical use of BPs in digestive cancers is limited, preclinical studies across this diverse disease group consistently show that BPs exert antitumor effects as monotherapies, and may increase the efficacy of other systemic agents when given in combination. The combination of anti-HER agents and NBPs is of particular interest given recent mechanistic insights into the interactions of BPs with the HER family as well as the prevalence of HER aberrations in digestive malignancies. Studies to assess the clinical relevance of BPs as antineoplastic adjuncts in digestive cancers represent a largely untapped research opportunity.

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