ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2018 May 15; 10(5): 108-123

Published by Baishideng Publishing Group Inc

WJGO

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 10 Number 5 May 15, 2018

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INDEXING/ABSTRACTING

World Journal of Gastrointestinal Oncology is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

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E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
May 15, 2018

INSTRUCTIONS TO AUTHORS
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ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2018 May 15; 10(5): 108-114

DOI: 10.4251/wjgo.v10.i5.108

ISSN 1948-5204 (online)

MINIREVIEWS

Targeted therapy or immunotherapy? Optimal treatment in hepatocellular carcinoma

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Author contributions: Wu J provided the concept, the outline, the structure, major references for this manuscript and provided critical revisions for this manuscript; Contratto M drafted the majority of the manuscript and incorporated several revisions based on feedback from Wu J; all authors approved the final manuscript.

Conflict-of-interest statement: There is no conflict of interest.

Manuscript source: Invited manuscript

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Received: February 5, 2018
Peer-review started: February 7, 2018
First decision: March 8, 2018
Revised: March 14, 2018
Accepted: April 10, 2018
Article in press: April 11, 2018
Published online: May 15, 2018

Abstract

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer mortality in the United States and the second leading cause of cancer mortality worldwide. Sorafenib is the only food and drug administration (FDA) approved as first line systemic treatment in HCC. Regorafenib and nivolumab are the only FDA approved second line treatment after progression on sorafenib. We will discuss all potential first and second line options in HCC. In addition, we also will explore sequencing treatment options in HCC, and examine biomarkers that can potentially predict benefits from treatments such as immune checkpoint inhibitor. This minireview summarizes potential treatments in HCC based on clinical trials that have been published in manuscript or abstract format from 1994-2018.

Key words: Sequencing treatment; Sorafenib; Hepatocellular carcinoma treatments; Nivolumab; Regorafenib; Lenvatinib; Cabozantinib; Immunotherapy; Biomarker; Pembrolizumab; Ramucirumab; Alpha-fetoprotein; Neoantigen; Tumor mutational burden; Interferon-gamma

Core tip: Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer mortality in the United States and the second leading cause of cancer mortality worldwide. There are some potential treatment options for first and second line HCC, there are also new biomarkers that can predict benefits from treatments such as immune checkpoint inhibitors.

Contratto M, Wu J. Targeted therapy or immunotherapy? Optimal treatment in hepatocellular carcinoma. *World J Gastrointest Oncol* 2018; 10(5): 108-114 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i5/108.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i5.108

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth leading

cause of cancer mortality in the United States and the second leading cause of cancer mortality worldwide[1]. Sorafenib has been the only food and drug administration (FDA) approved first line treatment in HCC since 2007. Lenvatinib is another promising treatment in first line HCC, demonstrated non-inferiority in median overall survival (mOS) compared to sorafenib[2]. Nivolumab also might have activity in first line HCC. In the second line treatment of HCC, there are 2 FDA approved medications regorafenib and nivolumab. In addition, other targeted therapies such as cabozantinib or pembrolizumab might be beneficial in second line treatment of HCC.

We will discuss the options of systemic treatment in HCC both for first and second line, the optimal sequencing of treatments, their side effects, and potential biomarkers that may predict benefits of therapy.

FIRST LINE SYSTEMIC TREATMENT IN HCC

Sorafenib is a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor-beta, KIT and RAF/ mitogen-activated protein/MEK. In the phase Ⅲ (SHARP trial) of 602 HCC patients with Child Pugh Class A (preserved liver function), mOS in sorafenib was 10.7 mo[3]. Although it is the first line and only therapy that improves mOS in first line patients, most of patients could not tolerate at the full dose of sorafenib due to the side effects. In the oncology community, most patients are started on lower dose, for example 200 mg PO BID with potential up titration. The most common adverse events (AEs) were diarrhea (39%), fatigue (22%), hand-foot skin reaction (21%), rash (16%), and alopecia (14%)[3]. The common grade 3/4 AEs were hypophosphatemia (11%), diarrhea (8%), hand-foot skin reaction (8%), thrombocytopenia (4%), and hypertension (2%)[3]. Even though there was no difference in survival benefits whether or not patients are started at a full dose (400 mg BID) or reduced dose (200 mg BID), it improved cost-effective in sorafenib treatment[4,5]. Therefore sorafenib is most beneficial for patients with Child Pugh Class A with preserved liver function. In a retrospective subanalyses of phase Ⅲ SHARP study, sorafenib has shown mOS of 14 mo in HCV patients[6]. In the SHARP study, the top 3 risk factors for HCC in the sorafenib group were Hepatitis C (29%), alcohol (26%), and hepatitis B (19%). In the phase Ⅲ of Asia Pacific study in 226 HCC patients with Child Pugh Class A, up to 73% patients were HBV positive. This study reported the mOS was 6.5 mo in sorafenib *vs* 4.2 mo in placebo group[7]. In a retrospective study of 59 unresectable HCC patients who received sorafenib that included Child Pugh Class A (26), B (23), and C (10)[8]. The mOS were 8.3, 4.3, and 1.5 mo, respectively[8]. In this study, the top 3 risk factors for HCC were alcohol (38%) and viral hepatitis B/C (26%). This retrospective study suggested that sorafenib may exert the maximum benefit in Child Pugh Class A patient, regardless of etiology for HCC.

Some of the side effects emerged from sorafenib suggested that hypertension (HTN) and diarrhea may be correlated with efficacy. In a retrospective study in 41 HCC patients (Child Pugh Class A/B, 25/16 patients), showed development of HTN led to better response to sorafenib treatment, with mOS of 18.2 mo *vs* 4.5 mo in patients without HTN[9]. Another retrospective study in 112 patients with advanced HCC showed that diarrhea can also predict the response to sorafenib treatment as well. Patients with diarrhea demonstrated longer mOS of 14.1 mo *vs* 7.1 mo when compared to patients without diarrhea[10].

POTENTIAL FIRST LINE SYSTEMIC TREATMENT OPTIONS IN HCC

Lenvatinib is a multiple kinase inhibitor that inhibits VEGFR 1-3, fibroblast growth factor receptor 1-4, platelet derived growth factor receptor (PDGFR) alpha, c-Kit and RET proto-oncogene. In the randomized phase Ⅲ (REFLECT) study of lenvatinib *vs* sorafenib in first line treatment of unresectable HCC in 954 patients (1:1) with Child Pugh Class A, it showed mOS in lenvatinib *vs* sorafenib was 13.6 mo and 12.3 mo, respectively. It met its primary endpoint of non-inferiority and it achieved the secondary endpoints with the median progression free survival (PFS) of 7.4 mo *vs* 3.7 mo and the time to progression (TTP) was 8.9 mo *vs* 3.7 mo[2]. The most common AEs were hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), and fatigue (30%)[2]. The common grade 3/4 AEs were hypertension (23%), decreased weight (8%), decreased platelet count (6%), elevated aspartate aminotransferase (5%), and decreased appetite (5%)[2]. The usage dose is oral 8 mg (weight < 60 kg) or 12 mg (weight ⩾ 60 kg) once daily. In the phase 2 study of lenvatinib in 46 HCC patients with Child Pugh Class A, the objective response rate (ORR) was 37%[11]. The most common causes of HCC in phase 2 study were Hepatitis C (58.7%), Hepatitis B (32.6%), and Alcohol (4.3%).

Nivolumab is an immune checkpoint inhibitor that inhibits PD-1. In a phase Ⅰ/Ⅱ study (CHECKMATE 040) of nivolumab in advanced HCC patients in the dose-expansion phase, there were 56 sorafenib naïve patients. All patients were uninfected with viral hepatitis (55 with Child Pugh Class A and only 1 Child Pugh Class B)[12]. This study showed ORR of 23% and OS rate of 82% at 9 mo[12]. Nivolumab showed 23% of partial response (PR) in HCC sorafenib naïve patients, it could be considered as a potential first line treatment[12]. It demonstrated that nivolumab might be beneficial for first line treatment in HCC patients. A phase Ⅲ study of nivolumab compared to sorafenib as a first line treatment is ongoing.

SECOND LINE TREATMENT OPTIONS IN HCC

Regorafenib, is an oral multikinase inhibitor specifically inhibits VEGFR-1, 2, 3. It was approved by FDA on April

27, 2017 as a second line treatment in HCC patients who have been previously progressed with sorafenib. In this study, the median treatment time on first line sorafenib was 7.8 mo for both patient groups[13]. This study showed mOS of 10.6 mo in regorafenib groups (379) *vs* 7.8 mo in placebo groups (194)[13]. The median PFS was 3.1 mo in regorafenib *vs* 1.5 mo in placebo group[13]. The ORR in regorafenib group was 11%[13]. In the phase Ⅲ (RESORCE) study of regorafenib in 573 HCC patients with Child Pugh Class A, the most common AEs were hand-foot skin reaction (52%), diarrhea (33%), fatigue (29%), anorexia (24%), and hypertension (23%)[13]. The common grade 3/4 AEs were hypertension (13%), hand-foot skin reaction (13%), fatigue (6%), increased blood bilirubin (6%), and increased AST (4%)[13]. The etiologies of HCC in this study were hepatitis B (38%), alcohol use (24%), and hepatitis C (21%)[13]. In this study (RESORCE) showed that 199 patients out of 374 patients who received regorafenib had experience of hand-foot skin reaction during cycle 1, these patients had better mOS of 14.1 mo *vs* 6.6 mo in patients who did not experience hand-foot skin reaction. It also showed HR of 0.52[14]. It suggests that hand-foot skin reaction should be managed properly to get a better response of regorafenib and mOS benefit.

Nivolumab, is an immunotherapy that inhibits PD-1. It was granted approval by FDA on September 22, 2017 as a second line systemic treatment in HCC patients who have been treated with or intolerant to sorafenib. The phase Ⅰ/Ⅱ study of nivolumab with dose escalation that included 48 patients with Child Pugh Class A and B7, in addition to dose expansion in 214 patients (Child Pugh Class A)[12]. In the dose-escalation phase, ORR was 15%, 6 mo and 9 mo OS rates were both 66%, and mOS was 15 mo[12]. In the dose expansion phase, ORR was 20%, 6 mo and 9 mo OS rates were 83% and 74%, only the group in sorafenib progressor without viral hepatitis reached mOS of 13.2 mo and the rest of the groups did not reach mOS[12]. In the dose expansion phase, the patients were divided into 113 patients without HBV or HCV (56 untreated/intolerant of sorafenib and 57 progressed post sorafenib)[12]. In addition, this phase also included 51 patients with HBV and 50 patients with HCV[12]. The study demonstrated transient decreased HCV RNA in some HCV infected patients and no reactivation in HBV infected patients. The most common AEs were fatigue (25%), pruritus (20%), diarrhea (18%), rash (11%), and increased AST level (11%)[12]. The grade 3/4 AEs were increased AST (4%), rash (2%), diarrhea (2%), and fatigue (2%)[12]. The dose is 3 mg/kg (240 mg) every 2 wk.

In a retrospective analysis of this study, PD-L1 was showed as biomarker that predicted response to nivolumab in 174 out of 214 patients. The ORR was 26% *vs* 19% in patients with PD-L1 ⩾ 1% compared with PD-L1 < 1%, it suggested that PD-L1 could be a potential biomarker associated with nivolumab treatment[12].

Cabozantinib is an oral tyrosine kinase inhibitor including VEGFR, MET, RET, KIT, and FLT3. In the phase Ⅲ (CELESTIAL) study of cabozantinib *vs* placebo in 707 HCC patients with Child Pugh Class A who previously received sorafenib[15]. The characteristics of the patients were the median age of patients was 64 years, 82% male patients, 38% HBV infected, 25% HCV infected, 78% had extrahepatic spread, 30% had macrovascular invasion, and 27% had received two prior systemic therapy[15]. This study has achieved mOS of 10.2 mo in cabozantinib *vs* 8 mo in placebo group[15]. It also achieved median PFS of 5.2 mo in cabozantinib *vs* 1.9 mo in placebo group, and ORR of 4% in cabozantinib group *vs* 0.4% in placebo group[15]. The most common grade 3/4 AEs were hand-foot syndrome (17%), HTN (16%), increased AST (12%), fatigue (10%), and diarrhea (10%)[15]. It suggested that cabozantinib has the potential to be an effective treatment for second line HCC.

Pembrolizumab is an immunotherapy that inhibits PD-1. In the Phase 2 study (KEYNOTE-224) of Pembrolizumab in 104 HCC patients with Child Pugh Class A who progressed on sorafenib treatment. The primary endpoint of this study was achieved with ORR of 16.3% with 1 CR[16]. The median PFS was 4.8 mo and the 6 mo PFS and OS rates were 43.1% and 77.9%, respectively[16]. About 94% of patients who responded, continue to respond at 6 mo[16]. The most common AEs were fatigue (21.2%) and increased AST (12.5%)[16]. The etiologies of HCC were HBV (21.2%) and HCV (26%)[16]. The grade 3-5 AE was reported in 25% of patient with 1 death due to ulcerative esophagitis[16]. This study showed that pembrolizumab might have a good response in advanced HCC patients who progressed on sorafenib.

Ramucirumab is a fully monoclonal antibody (IgG1) that inhibits VEGFR2. In the phase Ⅲ study of ramucirumab *vs* placebo as a second line treatment in 565 HCC patients with Child Pugh Class A (REACH)[17]. Eventhough there was no significantly improvement in mOS between patients who received ramucirumab *vs* placebo (9.2 mo *vs* 7.6 mo), ORR in ramucirumab group was higher than the placebo group (7% *vs* < 1%)[17]. The most common AEs were peripheral edema (36%), liver injury (30%), bleeding or haemorrhage (26%), ascites (22%), and fatigue (21%)[17]. The grade 3/4 AEs were liver injury (14%), hypertension (13%), ascites (5%), bleeding or haemorrhage (5%), and asthenia (5%)[17]. The etiologies of HCC in this study were Hepatitis B (35%) and Hepatitis C (27%)[17]. In the prespecified subgroup retrospective analysis of 250 patients with α-fetoprotein (AFP) ⩾ 400 ng/mL, the mOS was 7.8 mo (ramucirumab group) *vs* 4.2 mo (placebo group)[17]. It suggested that ramucirumab could be beneficial in HCC patients with AFP ⩾ 400 ng/mL. AFP can potentially be used as a biomarker to predict the response of ramucirumab treatment in HCC patients. A phase Ⅲ study looking for HCC patients with AFP ⩾ 400 ng/mL not prespecified is ongoing.

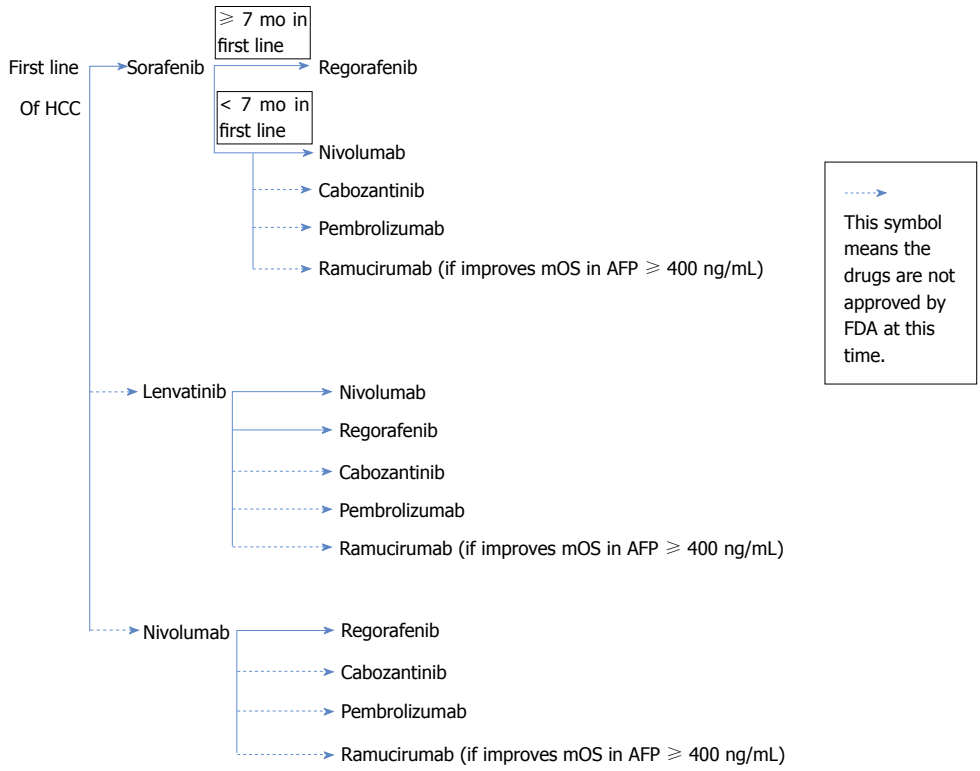

Figure 1 Potential sequencing treatment options in hepatocellular carcinoma. The only food and drug administration (FDA) approved for first line systemic treatment for hepatocellular carcinoma (HCC) is sorafenib. If patients tolerate sorafenib well and could stay on therapy for at least 7 mo, regorafenib (FDA approved) would be a preferred second line option. If patients could not tolerate sorafenib well or received less than 7 mo of treatment with sorafenib, the next second line options will be nivolumab (FDA approved) and could be cabozantinib or pembrolizumab after get approval by FDA. Another potential first line option will be lenvatinib or nivolumab after get approval by FDA. If patients progress on lenvatinib, then second line options will be nivolumab, regorafenib, cabozantinib, pembrolizumab. For patients who progress on nivolumab, then second line options will be regorafenib, cabozantinib, pembrolizumab. Another possible option of second line treatment after patients progress after the above first line treatment could be ramucirumab if the phase Ⅲ study shows improvement of mOS in HCC patients with AFP ≥ 400 ng/mL. FDA: Food and drug administration; mOS: Median overall survival; RR: Response rate.

SEQUENCING TREATMENTS IN HCC IN THE FUTURE

Sorafenib is the only FDA approved first line treatment in HCC. It is beneficial in HCC patients with Child Pugh Class A and especially in patients with HCV. As demonstrated in a retrospective analysis of HCV patients which comprised 29% of the total patient populations in SHARP study, the mOS was 14 mo, while mOS of the overall population was only 10.9 mo. When patients experience side effects such as HTN or diarrhea, these side effects should be managed aggressively to minimize premature discontinuation of sorafenib. In a two retrospective studies in patients who had HTN or diarrhea were linked to a better mOS compared to patients who did not experience HTN or diarrhea. For instance, the mOS in HTN group was 18.2 mo *vs* 4.5 mo in group without HTN, the mOS in patients with diarrhea was 14.1 mo *vs* 7.1 mo in patients without diarrhea (Figure 1).

If patients with Child Pugh Class A tolerate sorafenib well in the first line setting, regorafenib would be a good choice as a second line treatment due to similar toxicities profiles of the two medications. Regorafenib was only studied in patients with Child Pugh Class A. For patients who have difficulty tolerating toxicities of sorafenib, nivolumab could be a good option as a second line treatment, it achieved ORR of 15%-20%. Nivolumab will be beneficial in patients with Child Pugh Class A/B7. Nivolumab achieved higher RR in PD-L1 ≥ 1% (positive) compared to tumors with PD-L1 < 1% (negative), 26% and 19% respectively. However nivolumab does not seem to offer differential outcomes regardless of the length of treatment on first line therapy. Even though cabozantinib or pembrolizumab or ramucirumab have not been FDA approved at this time. Once become FDA approved, then cabozantinib or pembrolizumab could be other second line options. If the phaseⅢstudy in HCC patients with AFP ≥ 400 ng/mL shows improvement mOS with ramucirumab, then the strategy for second line treatment may include testing of AFP. For patients with AFP ≥ 400 ng/mL, ramucirumab could be a second line option.

Lenvatinib has shown non-inferiority to sorafenib in a phase Ⅲ study, therefore it would be a first line treatment in HCC if granted FDA approval. It could be a good alternate to sorafenib for patients who prefer to have less hand-foot syndrome and/or diarrhea. Once patients progress, the second line treatment options are nivolumab (in patients with Child Pugh Class A or B7 only and PD-L1 +) and regorafenib (in Child Pugh Class

A). Other potential second line options are cabozantinib, pembrolizumab, or ramucirumab.

Nivolumab as first line treatment if granted FDA approval, it will be beneficial for patients who have no contraindication to immunotherapy or who have severe HTN at baseline. If patients could not tolerate or progressed while on nivolumab, the second line options could be regorafenib. Other potential second line options are cabozantinib, pembrolizumab, or ramucirumab.

POTENTIAL BIOMARKERS TO MAXIMIZE THE RESPONSE OF TREATMENT IN HCC

AFP

AFP stands for alpha-feto protein, it is used as a diagnostic and prognosis marker in HCC patients. In a single-institution prospective study, preoperative value of AFP > 400 ng/mL in 108 resectable HCC patients, correlated with higher recurrence rates and lower survival rates at 2 years[18]. In a prespecified group of 250 HCC patients in a phase Ⅲ ramucirumab trial (REACH) with a baseline AFP ⩾ 400 ng/mL, mOS of ramucirumab and placebo was 7.8 mo and 4.2 mo, respectively[17]. In the group (310 patients) where baseline AFP < 400 ng/mL, there was no difference in mOS between ramucirumab and placebo. Therefore, AFP could be used as a marker to predict response with ramucirumab treatment. Phase Ⅲ of ramucirumab study is ongoing in HCC patients with AFP ⩾ 400 ng/mL and the mOS benefit needs to be validated in patients with AFP ⩾ 400 ng/mL, once the preliminary data is available.

PD-L1

A programmed death ligand-1 could be a potential biomarker to predict the efficacy of immune checkpoint inhibitors. PD-L1 can be detected using several assays, and the definition of PD-L1 positivity and the methodology of measuring PD-L1 are required to understand about the role of PD-L1 in HCC[19]. In a phase Ⅱ dose expansion cohort study of nivolumab in HCC patients either progressed or intolerant of sorafenib, RR was 26% *vs* 19% in patients with PD ⩾ 1% and PD-L1 < 1%, respectively[12]. PD-L1 ⩾ 1% therefore appears to indicate higher RR in HCC and it also predicts response of nivolumab treatment with mOS benefit.

FUTURE DIRECTION BIOMARKERS

Neoantigen

A tumor-specific mutated peptides on the surface of cancer cells initiate neoantigen production. Each tumor cell causes genetic mutations due to alteration of peptides (amino acid sequencing), it produces neoantigen signature that contains four amino acid strings of peptides[20]. Neoantigen signature is seen in patients with long term clinical benefit of therapy (no evidence of disease for > 6 mo)[20]. Neoantigen was investigated using whole exome sequencing in DNA of tumor cell. Neoantigen can be used as a biomarker to predict the response to immune checkpoint inhibitor treatment. The higher number of neoantigen in a tumor that binds to major histocompatibility complex (MHC) class Ⅰ, it would be recognized easier by T cells to activate T cells. A prospective study of 18 non-small cell lung cancer (NSCLC) samples from patients who received pembrolizumab (anti-PD-1, an immunotherapy), high mutational burden related to high neoantigen (median of 112 candidate neoantigen per tumor) and associated with improvement of PFS for 14.5 mo[21]. This study showed high mutational burden at least 200 nonsynonymous mutations (mutations that altered protein in cancer cells) per sample, it related to durable clinical benefit (partial or stable response > 6 mo). High mutational burden by itself was not enough to predict durable clinical benefit, because in a few patients without durable clinical benefit also had high mutational burden. In addition to high mutational burden, high number of neoantigen was a better prediction of treatment response. It showed better PFS in patients with high neoantigen compared to low neoantigen group, with PFS of 14.5 mo *vs* 3.5 mo, respectively[21]. Another prospective study in 64 stageⅣmelanoma patients who received ipilimumab or tremelimumab (anti-CTLA-4) demonstrated long term clinical benefit in 11 out of 25 patients with high number of mutational load, in addition 14 patients with high number of mutational load without long term clinical benefit[20]. In the second set of 39 melanoma patients who received anti-CTLA-4, 25 patients with high neoantigen had long term clinical benefit to anti-CTLA-4[20].

Tumor mutational burden

Tumor mutational burden (TMB) refers to DNA sample that can be detected in blood, and it is considered one example liquid biopsy. This non-invasive test is helpful and convenience especially if tumor tissue is inadequate. This biomarker might help to predict the response of immune checkpoint inhibitor. In a retrospective analysis of atezolizumab (anti-PD-L1) in NSCLC patients, blood was used to extract TMB to predict benefit in patients who received atezolizumab. It included 211 NSCLC patients in POPLAR and 583 NSCLC patients in OAK trial[22]. The TMB was minimum 10 single nucleotide variants (SNV) from cell free-DNA in plasma. In the POPLAR study, patients with TMB ⩾ 10, the atezolizumab group showed better PFS hazard ratio (HR) of 0.68 and OS HR of 0.59 compared to docetaxel group[22]. In the OAK study, PFS and OS were also better in the atezolizumab group compared to docetaxel group with HR of 0.73 and 0.69, respectively[22]. From this data, tumor mutational burden could be beneficial as a biomarker for the efficacy of immune checkpoint inhibitor. Prospective studies using TMB in NSCLC patients are ongoing. It needs further investigation for HCC patients in the future.

Interferon gamma

A cytokine that is produced by several cells including CD4+ T helper cell type 1 (Th1 cells), CD8+ cytotoxic T cell, macrophage, mucosal epithelial cell, natural killer cell (NK), and NK T cell[23-25]. It inhibits cellular proliferation and causes apoptosis[26]. A study in 48 HCC patients who received curative treatment (surgery/RFA), a higher risk of tumor recurrence was observed in patients with lower levels of interferon gamma (IFN-γ)[27]. IFN-γ can therefore be a potential marker to predict HCC recurrence. In two prospective studies from 17 NSCLC and 21 melanoma patients who received pembrolizumab (anti-PD-1), these studies analyzed IFN-γ mRNA to predict response treatment of pembrolizumab. It showed longer PFS and OS in NSCLC patients with high level *vs* low level of IFN-γ (5.12 *vs* 2 mo; 10.15 *vs* 4.86 mo). It also showed longer PFS in melanoma patients with high level *vs* low level of IFN-γ (4.99 mo *vs* 1.86 mo)[28].

CONCLUSION

HCC is the second leading cause of cancer mortality worldwide. Sorafenib is the only FDA approved first line treatment in unresectable HCC. Sorafenib has shown median OS response in HCC patients with HCV infection. There are others potential first line treatments in HCC such as lenvatinib and nivolumab, although not FDA approved, hold great promise based on phase Ⅲ studies. The second line treatments of HCC patients who progressed or intolerant to sorafenib, include regorafenib and nivolumab. Regorafenib demonstrated higher median OS in HCC patients who tolerated sorafenib for at least 7 mo. Nivolumab has been reported to be more beneficial in HCC patients with Child Pugh Class A/B7, and achieved higher RR in patients with PD-L1 ⩾ 1%. Other potential options for second line treatments are cabozantinib (phase Ⅲ) or pembrolizumab (phase Ⅱ).

There are two current biomarkers that used to predict response of treatment such as PD-L1 and AFP. For instance, PD-L1 indicates higher RR in nivolumab study, and AFP ⩾ 400 ng/mL shows a trend for higher median OS in ramucirumab subgroup analysis phase Ⅲ study. In addition, other future biomarkers that might be used to predict response of treatment are neoantigens, tumor mutational burden and IFN-γ. These biomarkers need further validation in large randomized clinical trials.

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P- Reviewer: Jin B, Ma J, Neninger E, Tabll AA, Wakao H **S- Editor**: Cui LJ **L- Editor**: A **E- Editor**: Tan WW

World Journal of Gastrointestinal Oncology

Submit a Manuscript: http://www.f6publishing.com

DOI: 10.4251/wjgo.v10.i5.115

World J Gastrointest Oncol 2018 May; 10(5): 115-123

ISSN 1948-5204 (online)

MINIREVIEWS

Risk of gastric cancer development after eradication of *Helicobacter pylori*

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Author contributions: All authors contributed equally to this paper with literature review and analysis, drafting and critical revision and editing, and approval of the final version of this article.

Conflict-of-interest statement: Wai K Leung has received honorarium for attending advisory board meetings of Boehringer Ingelheim and Takeda.

Manuscript source: Invited manuscript

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Received: February 7, 2018
Peer-review started: February 7, 2018
First decision: March 15, 2018
Revised: March 23, 2018
Accepted: April 15, 2018
Article in press: April 16, 2018
Published online: May 15, 2018

Abstract

Helicobacter pylori (*H. pylori*) infection is the most important risk factor for gastric cancer (GC) development through the Correa's gastric carcinogenesis cascade. However, *H. pylori* eradication alone does not eliminate GC, as pre-neoplastic lesions (atrophic gastritis, intestinal metaplasia and dysplasia) may have already developed in some patients. It is therefore necessary to identify patients at high-risk for gastric cancer after *H. pylori* eradication to streamline the management plan. If the patients have not undergone endoscopy with histologic assessment, the identification of certain clinical risk factors and non-invasive testing (serum pepsinogen) can predict the risk of atrophic gastritis. For those with suspected atrophic gastritis, further risk stratification by endoscopy with histologic assessment according to validated histologic staging systems would be advisable. Patients with higher stages may require long-term endoscopic surveillance. Apart from secondary prevention to reduce deaths by diagnosing GC at an early stage, identifying medications that could potentially modify the GC risk would be desirable. The potential roles of a number of medications have been suggested by various studies, including proton pump inhibitors (PPIs), aspirin, statins and metformin. However, there are currently no randomized clinical trials to address the impact of these medications on GC risk after *H. pylori* eradication. In addition, most of these studies failed to adjust for the effect of concurrent medications on GC risk. Recently, large population-based retrospective cohort studies have shown that PPIs were associated with an increased GC risk after *H. pylori* eradication, while aspirin was associated with a lower risk. The roles of other agents in reducing GC risk after *H. pylori* eradication remain to be determined.

Key words: Gastric adenocarcinoma; Stomach cancer; *Helicobacter pylori*; Chemoprevention; Intestinal metaplasia

Core tip: Although *helicobacter pylori* (*H. pylori*)

infection is the most important risk factor for gastric cancer (GC) development, eradication of this bacteria does not guarantee the elimination of GC risk, as pre-neoplastic lesions may have already developed. It is therefore necessary to identify patients at high-risk for GC after *H. pylori* eradication by either endoscopy with histologic assessment or non-invasive testing. Long-term endoscopic surveillance is advisable for high-risk patients. Future studies are necessary to investigate medications that may modify the GC risk after *H. pylori* eradication.

Cheung KS, Leung WK. Risk of gastric cancer development after eradication of *Helicobacter pylori*. *World J Gastrointest Oncol* 2018; 10(5): 115-123 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i5/115.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i5.115

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide, with an estimation of 952000 new cases (6.8% of all incident cancer cases) in 2012[1]. The disease burden is particularly high in East Asian countries where around half of the new cases are diagnosed. It is the third leading cause of cancer related mortality in the world, with 723000 deaths (8.8% of all cancer deaths) in a year. Around two-thirds of patients are diagnosed with GC at an advanced stage when curative surgery is not possible[2,3]. Despite the advances in surgery and chemotherapy, the prognosis remains dismal in patients with advanced disease, with a median survival of less than one year.

The global prevalence of *Helicobacter pylori* (*H. pylori*) infection in adults ranges from 19% to 88%[4]. *H. pylori* infection is one of the major risk factors for GC development (a relative risk of 2.8 as shown in a recent meta-analysis)[5]. It is estimated that *H. pylori* infection attributes to 89% of non-cardia GC cases, which in turn accounts for 78% of all GC cases[6]. *H. pylori* is classified by the International Agency for Research on Cancer of the World Health Organization as class I human carcinogen[7]. It is postulated that *H. pylori* infection triggers and promotes the Correa's cancer cascade[8]– a multistep process involving sequential changes of the gastric mucosa from chronic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia and finally adenocarcinoma. Atrophic gastritis, intestinal metaplasia and dysplasia are considered to be pre-neoplastic lesions. In a population-based cohort study, the risk of GC was increased in patients with atrophic gastritis, intestinal metaplasia and dysplasia as compared to those with normal gastric mucosa by a hazard ratio (HR) of 4.5, 6.2 and 10.9, respectively[9].

H. PYLORI ASSOCIATED GC

There are multiple pathways by which *H. pylori* leads to GC development. *H. pylori* incites acute-on-chronic inflammation, leading to a high turnover rate of gastric epithelium as well as a microenvironment in which high levels of reactive oxygen and nitrogen radicals promote persistent DNA damage[10-13]. *H. pylori* can also induce epigenetic changes including CpG island methylation of tumor suppressor genes such as E-cadherin[14,15]. The aberrant expression of activation-induced cytidine deaminase *via* the effect of nuclear factor (NF)-κB can alter nucleotides in the tumor-related genes[16,17]. The induction of double-stranded DNA breaks and alteration of microRNAs expression further contribute to the genetic instability[11,18]. The interplay between *H. pylori,* gastric microbiome and the exogenous factors in producing carcinogens further adds complexity to the *H. pylori*-induced carcinogenesis[18]. *H. pylori* eradication can reduce or even eliminate gastric mucosal inflammation and reverse the *H. pylori*-associated molecular events[15,18].

GC AFTER *H. PYLORI* ERADICATION

Although *H. pylori* is a major risk factor of GC, eradication of *H. pylori* does not completely eliminate the risk of subsequent GC development. It has been shown that *H. pylori* eradication could only reduce GC by 33%-47%[19,20]. The fact that a significant proportion of *H. pylori*-eradicated subjects progress to develop GC is likely related to the baseline gastric histology at the time of eradication. The development of pre-neoplastic lesions including atrophic gastritis, intestinal metaplasia and dysplasia undermines the effect of *H. pylori* eradication in reducing GC[21,22]. In a prospective, randomized study involving 1630 *H. pylori*-infected subjects conducted by Wong *et al*[21], the beneficial effect of *H. pylori* eradication was limited to patients without baseline pre-neoplastic lesions (atrophic gastritis, intestinal metaplasia and dysplasia). No GC was diagnosed among patients who received *H. pylori* eradication therapy without pre-neoplastic lesions during a follow-up of 7.5 years. A meta-analysis of 10 studies involving 7955 patients by Chen *et al*[22] also showed similar findings.

H. pylori eradication is found to reverse chronic gastritis in the majority of patients and atrophic gastritis in some patients[23-25], but not for intestinal metaplasia[24,26]. The presence of intestinal metaplasia is therefore considered to be a "point of no return" in the GC cascade. However, *H. pylori* eradication has been shown to slow the progression of intestinal metaplasia to GC[25,27]. A study of 2258 patients with a much longer follow-up duration (up to 15 years) showed that *H. pylori* eradication reduced GC risk even in those with intestinal metaplasia and dysplasia[28]. In concordance with this study, a randomized controlled trial of 544 patients concluded that *H. pylori* eradication after endoscopic resection of early GC could reduce the risk of metachronous GC by 65%[29]. Since most of these patients with early GC would have concurrent pre-neoplastic lesions in the stomach, the findings would

support the potential benefits of *H. pylori* eradication to prevent GC development even in the presence of advanced gastric histology.

A recent nationwide population-based study from Sweden showed that treatment for *H. pylori* could reduce GC and non-cardia GC development when compared to background population[30]. Overall, about 0.2% of patients developed GC after *H. pylori* treatment. However, the risk reduction was only apparent 5 years after *H. pylori* eradication treatment (standardized incidence ratio of 0.31), suggesting a long lag time of benefits by chemoprevention.

SURVEILLANCE FOR HIGH-RISK PATIENTS AFTER *H. PYLORI* ERADICATION

Eradication of *H. pylori* before the development of atrophic gastritis can nearly eliminate GC risk[31]. As discussed, among patients who have already developed atrophic gastritis, eradication of *H. pylori* can only halt and partially reverse the progression of gastric mucosal damage, and therefore this group of patients is still at increased risk for GC development. According to the Kyoto Global Consensus statement[32], patients with *H. pylori* infection diagnosed non-invasively and at risk for atrophic gastritis should undergo endoscopy for histological assessment. These risk factors include age range in which atrophic gastritis are prevalent in that particular population, a prior history of gastric ulcer, a pretreatment serum pepsinogen Ⅰ level of less than 70 ng/mL and a pepsinogen Ⅰ : Ⅱ ratio of less than 3. The degree and extent of atrophic gastritis and intestinal metaplasia are important in predicting subsequent GC risk. Two validated histologic staging systems, Operative Link for Gastritis Assessment (OLGA)[33] and Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM)[34], have been proposed for further risk stratification. Those with OLGA or OLGIM stages Ⅲ-Ⅳ are considered to be at high risk of GC development, and may be considered for a long-term endoscopic surveillance program[31]. Surveillance programs are considered to be cost effective only in this group of high-risk patients[32,35,36]. The aims of secondary prevention programs are to remove intraepithelial lesions and early GC before the lesions become invasive, thereby reducing GC-related deaths[31,32]. Currently, there are insufficient data to guide the optimal management strategies for patients with lower OLGA and OLGIM stages. Even the optimal surveillance intervals for high risk patients are based on expert opinions rather than data from clinical trials[37].

ROLES OF MEDICATIONS IN GC DEVELOPMENT AFTER *H. PYLORI* ERADICATION

There are still sparse data on the modifiable risk factors for GC after *H. pylori* eradication. Increasing evidence has emerged showing that certain medications may increase GC risk, while some are shown to reduce cancer risk. However, the majority of these studies included both *H. pylori*-infected and *H. pylori*-negative subjects. In the following sections, medications that could potentially modify GC risk after *H. pylori* eradication, including proton pump inhibitors (PPIs), aspirin, cyclooxygenase-2 (COX-2) inhibitors, statins, metformin as well as lifestyle factors will be discussed. Their effects are summarized in Table 1.

Proton pump inhibitors

Since its introduction in the 1980s, PPIs have become one of the most commonly prescribed medications worldwide[38]. PPIs lead to profound acid suppression which could worsen atrophic gastritis[39], particularly in *H. pylori*-infected subjects[40]. In addition, the increase in gastrin (a potent growth factor that has trophic effect on gastric mucosa) in response to the hypochlorhydria would stimulate enterochromaffin-like cell hyperplasia[40]. A meta-analysis of four studies (one cohort and three case-control studies) showed that the risk of GC was increased by 43% among PPI users[41]. However, the *H. pylori* status was unknown in these studies, and multiple biases including protopathic and indication biases were present.

Recently, we conducted a territory-wide retrospective cohort study recruiting 63397 *H. pylori*-eradicated subjects[42]. PPIs use (defined as at least weekly use) was shown to be associated with an increased GC risk (HR = 2.44) even after *H. pylori* eradication, while histamine-2 receptor antagonists (H2RA) were not a significant risk factor. Compared with non-PPIs use, the risk increased with increasing frequency (HR 2.43 for weekly to less than daily use, and HR 4.55 for daily use) and duration of PPIs use (HR = 5.04, 6.65 and 8.3 for ⩾ 1 year, ⩾ 2 years and ⩾ 3 years, respectively). The adjusted absolute risk difference for PPIs *vs* non-PPIs use was 4.29 excess GC cases per 10000 person-years. H2RA was chosen as a negative control exposure in this study to address the issue of indication bias. Prescriptions of PPIs and H2RA within six months prior to GC diagnosis were excluded to reduce protopathic bias. One intriguing observation from this study was that the cohort of PPIs users who had not received *H. pylori* eradication therapy had the lowest incidence rate of GC (0.8 per 10000 person-years) when compared to that of the two *H. pylori*-eradicated cohorts with and without PPIs use (8.1 and 2.9 per 10000 person-years, respectively). It thus appears that prior *H. pylori* infection is still a more important risk factor than PPIs use in the determination of GC risk, and PPIs increase GC risk only in those with baseline pre-neoplastic lesions induced by prior *H. pylori* infection. The study, however, did not investigate whether the increased GC risk existed for all kinds of PPIs.

Aspirin

Recent meta-analyses investigating the potential role of aspirin concluded that aspirin was associated with

Table 1 Pharmacological modalities to reduce risk of gastric preneoplastic lesions and/or cancer

References	Drugs	Study design	Number of subjects	Results
You *et al*[92], 2006	Vitamin and garlic supplement	Randomized controlled trial	3365	No protective effect
Leung *et al*[56], 2006	Rofecoxib	Randomized controlled trial	213	Regression of IM: (a) antrum (24.5% *vs* 26.9% for placebo) (b) corpus (4.3% *vs* 2.2% for placebo)
Wong *et al*[57], 2012	Celecoxib	Randomized controlled trial	1024	OR of IM regression: (a) celecoxib alone (OR = 1.72; 95%CI: 1.07-2.76) (b) H. pylori eradication followed by celecoxib (OR = 1.48; 95%CI: 0.91-2.40)
Cheung *et al*[53], 2018	Aspirin	Population-based retrospective cohort study	63605	PS-adjusted HR of GC: 0.30 (95%CI: 0.15-0.61)
Cheung *et al*[42], 2018	Proton pump inhibitors	Population-based retrospective cohort study	63397	PS-adjusted HR of GC: 2.44 (95%CI: 1.42-4.20)

IM: Intestinal metaplasia; OR: Odds ratio; PS: Propensity score; HR: Hazard ratio; GC: Gastric cancer.

a reduced GC risk in observational studies, while post-hoc analysis of randomized trials showed statistically non-significant trend favoring aspirin use[43,44]. The chemopreventive effect of aspirin is mediated *via* both cyclooxygenase (COX)-2 and non-COX related pathways, including phosphatidylinositol 3-kinase (PI3K)[45,46], NF-κB[47], Wnt-β-catenin, extracellular signal-regulated kinase (ERK) and activated protein1 (AP-1)[48].

However, most published data included both *H. pylori*-infected and *H. pylori*-negative subjects. A few studies showed that the chemopreventive effect of aspirin was higher in *H. pylori*-infected subjects on stratified analysis[49-51]. As shown in a case-control study, the chemopreventive effect of aspirin use was higher in *H. pylori*-infected subjects [odds ratio (OR) = 0.39] than in the whole cohort (OR = 0.60), and no statistically significant difference was noted for *H. pylori*-negative subjects[50]. Another population-based study from Sweden showed that the ORs were 0.70 for the whole cohort and 0.60 for *H. pylori*-infected subjects, again without statistically significant difference for *H. pylori*-negative subjects[51]. Similarly, a Taiwanese nationwide retrospective cohort study found that the HR of GC with regular use of non-steroidal anti-inflammatory drugs (NSAIDs) was lower for *H. pylori*-infected (HR = 0.52) than non-infected subjects (HR = 0.80)[52].

A recent territory-wide retrospective cohort study recruiting 63605 *H. pylori*-eradicated subjects showed that aspirin use (defined as at least weekly use) was associated with a reduced GC risk (HR = 0.30)[53]. The protective effect increased with increasing frequency, duration and dose of aspirin (all *P*-trend < 0.001), being most prominent in those who used aspirin daily (HR = 0.21), for at least 5 years (HR = 0.07) and at a dose of at least 100 mg (HR = 0.15). The protective effect of aspirin appeared to be larger in *H. pylori*-eradicated subjects (HR = 0.30) than that reported by a meta-analysis including both *H. pylori*-infected and *H. pylori*-negative subjects (pooled OR = 0.78)[43]. This should be interpreted with caution, however, as it is not a head-to-head comparison with different patient characteristics.

However, one of the major side effects of aspirin is gastrointestinal bleeding, and the risk-benefit profile of aspirin use on GC prevention in *H. pylori*-infected subject remains to be determined. The adjusted absolute risk difference was only 2.52 fewer GCs per 10000 person-years for aspirin users after *H. pylori* eradication[53]. Future studies to address the risk-benefit profile are warranted. Nonetheless, the evidence from this territory-wide cohort study may provide further support for aspirin use in the consideration of the risk-benefit profile of aspirin use in preventing cardiovascular events and various cancers. The United States Preventive Services Task Force favors the use of low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50 to 59 years who have a more than 10% 10-year risk of cardiovascular disease and are not at increased risk of bleeding[54].

COX-2 inhibitors

COX-2 is an enzyme involved in the conversion of arachidonic acid to prostaglandins, and its overexpression is found in gastric intestinal metaplasia and cancer[55]. Two randomized trials have been performed to evaluate the potential benefit of COX-2 inhibitors[56,57]. In the study of 213 *H. pylori*-eradicated subjects with intestinal metaplasia, the use of rofecoxib did not significantly regressed intestinal metaplasia and its severity over 2 years[56]. The study by Wong et al showed that celecoxib use for 2 years could regress advanced gastric lesions in *H. pylori*-infected subjects, but a synergistic effect was not observed in those who had *H. pylori* eradicated[57].

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is one of the key enzymes for cholesterol synthesis[58], and are widely used for the primary and secondary prevention of cardiovascular diseases. Besides, it has been proposed to have chemo-preventive effects on solid organ tumors in *in-vitro* studies, by halting cell-cycle progression[59], inducing

apoptosis[60], inhibiting angiogenesis[61], and inhibiting the growth of tumor cells[62].

To date no data from randomized clinical trials are available concerning the role of statins in GC prevention. A meta-analysis[63] of 11 studies (eight observational, three post-hoc analyses of 26 clinical trials) reported a significant reduction in GC risk with statin use (adjusted OR = 0.68), in a dose-dependent manner. However, conflicting results exist among observational studies, with some showing statins to be protective against GC[64-67], while no such benefit was observed in other studies[68-74]. This is likely due to the heterogeneity of different studies, and the recruitment of both *H. pylori*-infected and *H. pylori*-negative subjects. The confounding effect of *H. pylori* would significantly affect the causal relationship and the magnitude of any beneficial effect. Therefore, studies dedicated to investigate the chemopreventive effect of statin on GC after *H. pylori* eradication are warranted.

Metformin

An increased GC risk by around 19% among patients with diabetes mellitus (DM) was reported by a meta-analysis of 17 studies (11 cohort studies, six case-control studies)[75]. But among diabetic patients who take metformin, the GC risk appears to be lower[76]. The anti-cancer activity by metformin is proposed to be mediated by two pathways. First, as metformin is an insulin sensitizer, it reduces the production of insulin and insulin-growth factors (IGFs). Proliferation of cancer cells expressing IGF receptors is stimulated by the IGFs signaling pathway[77]. Second, the activation of AMP-activated protein kinase (AMPK) and the subsequent inhibition of the mammalian target of rapamycin pathway is shown to inhibit the growth of cancer cells[78].

A recent meta-analysis of seven cohort studies concluded that metformin use was associated with a reduced GC risk (HR = 0.76)[76]. However, significant heterogeneity was noted among these studies. The chemopreventive role of metformin remains controversial in clinical studies, as data from randomized clinical trials are not available. While a protective effect with varying effect estimate was shown for some studies[79-83], others failed to demonstrate such association[84,85]. The failure to adjust for *H. pylori* infection and the severity of DM further complicates the debate over this issue.

A population-based cohort study of 2603 Japanese subjects showed the GC risk was larger with higher hemoglobin A1c (HbA1c) levels[86]. The age- and sex-adjusted incidence of GC among individuals with HbA1c levels of 5.0%-5.9%, 6.0%-6.9% and ⩾ 7.0% were 2.5, 5.1, and 5.5 per 1000 person-years. *H. pylori* infection and a higher HbA1c level (⩾ 6.0%) had a synergistic effect on increasing GC risk. The protective effect of metformin on GC may therefore be due to a better DM control instead of the anti-cancer effects found in *in-vitro* studies. This study, however, did not adjust for the effect of various medications and comorbidities, and therefore the independent role of HbA1c level remains to be determined.

Future studies to include a homogenous group of patients (*i.e.*, only *H. pylori*-eradicated subjects) and factor in the effect of DM control (as reflected by HbA1c level) as well as medications that may modify cancer risk are crucial to investigate (1) the chemopreventive role of metformin in GC in diabetic patients; and (2) whether HbA1c is an independent risk factor for GC. As HbA1c is a time-varying covariate, not only the baseline HbA1c level but also the dynamics throughout the follow-up should be taken into consideration in order to derive a more precise effect estimate.

Lifestyle factors

Lifestyle factors that could potentially affect the risk of preneoplastic lesions and GC include smoking, alcohol use, high salt intake, vitamins and antioxidants. Concentrated salt intake is proposed to cause excessive cell replication (hence increased rate of endogenous mutations), to incur mucosal damage with associated inflammatory changes and to induce atrophic changes in gastric mucosa[87]. Ascorbic acid, on the other hand, is linked with a protective effect against intestinal metaplasia and GC by reducing the gastric pH[88]. Atrophic gastritis favors the proliferation of anerobic bacteria which reduce nitrate (abundant in various kinds of food) to nitrite, in turn reacting with other nitrogen-containing components to generate N-nitroso carcinogens.

However, data on the roles of these factors in *H. pylori*-eradicated subjects are lacking. A randomized control trial on *H. pylori* eradication showed that alcohol consumption (OR = 1.67) was independently associated with intestinal metaplasia progression[89]. Another study of more than 3000 Chinese subjects with baseline chronic atrophic gastritis showed that the risk of transition to dysplasia nearly doubled among smokers while the risk of intestinal metaplasia was mildly increased[90]. In another study involving 3433 patients, the risk of progression to dysplasia or GC increased with increasing years of cigarette smoking, but decreased among those with higher levels of ascorbic acid (OR = 0.2, highest *vs* lowest tertile)[91].

The roles of vitamin and antioxidant supplements also remain controversial as shown by a three-arm trial which randomized 3365 *H. pylori*-infected subjects to eradication therapy, vitamin supplement (vitamin C, vitamin E and selenium) and garlic supplement (aged garlic extract and steam-distilled garlic oil)[92]. While *H. pylori* treatment reduced the risk of preneoplastic lesions and GC, similar beneficial effect was not observed for vitamin or garlic supplements.

CONCLUSION

H. pylori infection is the most important risk factor for GC development. However, *H. pylori* eradication does not entirely eliminate the GC risk, as pre-neoplastic

lesions (atrophic gastritis, intestinal metaplasia and dysplasia) may have already developed. It is therefore necessary to identify patients at high risk for GC after *H. pylori* eradication to streamline the management plan. The detection of atrophic gastritis by non-invasive testing (serum pepsinogen) or endoscopy with histologic assessment, followed by further risk stratification with validated histologic staging systems (*e.g.*, OLGA and OLGIM) would be advisable. Patients with higher stages may require regular endoscopic surveillance. Apart from secondary prevention to reduce deaths by diagnosing GC at an early stage, identifying medications that could potentially modify the GC risk would be desirable. The potential roles of a number of medications have been suggested by various studies, including PPIs, aspirin, statins and metformin. However, several drawbacks need to be acknowledged. First, there are currently no randomized clinical trials to address the impact of these medications on GC risk. Second, the majority of these studies recruited both *H. pylori*-infected and *H. pylori*-negative subjects, but not specifically *H. pylori*-eradicated ones. In addition, previous studies failed to adjust for the effect of concurrent medications on GC risk. The failure to take into account the effect of *H. pylori* infection and concurrent medications will undoubtedly bias the causal relationship and the effect estimate. Recently, large population-based retrospective cohort studies have shown that PPIs were associated with an increased GC risk after *H. pylori* eradication, while aspirin was protective. The roles of statin and metformin in reducing GC risk after *H. pylori* eradication remain to be determined.

Owing to the relatively low incidence of GC and the long lag time of cancer development, investigating the potential modifiable factors (including medications) for GC development by randomized clinical trials would require a large sample size and long follow-up duration which are technically difficult and resource-intensive. Future research should focus on high-risk population including those with underlying pre-neoplastic lesions, family history of GC or those who have undergone endoscopic removal of early gastric tumors. Another research direction would be the use of population-based retrospective cohort study design for pharmaco-epidemiological studies on GC. As such, studies can be carried out in a short period of time with large sample size, despite the relatively rare incidence of GC. We have previously examined the effects of PPIs and aspirin among *H. pylori*-eradicated subjects in population-based retrospective cohort studies. There are still other potential chemopreventive agents that remain to be explored, for example, statins and metformin. The concept of "drug repurposing" has recently been advocated in the field of oncology: Currently approved drugs with a non-oncology primary purpose may be used for chemoprevention or as an adjunctive treatment. The use of population-based retrospective cohort studies can help in identifying potential drug candidates and directing the path to future randomized clinical trials.

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P- Reviewer: Fiori E, Kim HS **S- Editor**: Wang XJ **L- Editor**: A
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