REVIEW

Oral Conventional Synthetic Disease-Modifying Antirheumatic Drugs with Antineoplastic Potential: a Review

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ABSTRACT

There is an increasing trend of malignancy worldwide. Disease-modifying antirheumatic drugs (DMARDs) are the cornerstones for the treatment of immune-mediated inflammatory diseases (IMIDs), but risk of malignancy is a major concern for patients receiving DMARDs. In addition, many IMIDs already carry higher background risks of neoplasms. Recently, the black box warning of malignancies has been added for Janus kinase inhibitors. Also, the use of biologic DMARDs in patients with established malignancies is usually discouraged owing to exclusion of such patients in pivotal studies and, hence, lack of evidence. In contrast, some conventional synthetic DMARDs (csDMARDs) have been reported to show antineoplastic properties and can be beneficial for patients with cancer. Among the csDMARDs, chloroquine and hydroxychloroquine have been the most extensively studied, and methotrexate is an established chemotherapeutic agent. Even cyclosporine A, a well-known drug associated with cancer risk, can potentiate the effect of some chemotherapeutic agents. We review the possible mechanisms behind and clinical evidence of the antineoplastic activities of csDMARDs, including chloroquine and hydroxychloroquine, cyclosporine, leflunomide, mycophenolate mofetil, mycophenolic acid, methotrexate, sulfasalazine, and thiopurines. This knowledge may guide physicians in the choice of csDMARDs for patients with concurrent IMIDs and malignancies.

Keywords: DMARDs; Cancer; Chloroquine and hydroxychloroquine; Cyclosporine; Leflunomide; Mycophenolate mofetil; Mycophenolic acid; Methotrexate; Sulfasalazine; Thiopurine

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Key Summary Points

csDMARDs still constitute the cornerstone in the treatment of immune-based inflammatory diseases in the era of biologics.

The use of biologic DMARDs in patients with established malignancies is usually discouraged owing to lack of evidence.

Many csDMARDs, especially chloroquine (CQ)/hydroxychloroquine (HCQ) and methotrexate (MTX), have established antineoplastic effects, either alone or in combination with chemotherapeutic agents.

Knowledge of the antineoplastic potentials of csDMARDs may guide physicians in the choice of csDMARDs for patients with concurrent IMIDs and malignancies.

INTRODUCTION

Disease-modifying antirheumatic drugs (DMARDs) are often referred to as immuno-suppressants or immunomodulators. Their antiinflammatory effect improves the symptoms and reduces the damage caused by rheumatic diseases [1]. However, the immunosuppressive property of DMARDs raises concern for the development of malignancy. It is especially important in view of the increasing number of patients with malignancy worldwide, mainly due to the aging population.

DMARDs can be further classified as conventional synthetic (csDMARDs), biologic (bDMARDs), and targeted synthetic [tsDMARDs, e.g., Janus kinase (JAK) inhibitors and phosphodiesterase-4 inhibitors]. csDMARDs are small molecules, for instance, azathioprine (AZA), chloroquine (CQ), hydroxychloroquine (HCQ), cyclosporine A (CSA), mycophenolate mofetil (MMF), mycophenolic acid (MPA), leflunomide, and sulfasalazine (SSZ). bDMARDs are monoclonal antibodies or fusion proteins developed to block specific molecules on immune cells or cytokines (IL-6, IL-1, TNF-α, etc.) [2].

Recently, the US Food and Drug Administration (FDA) issued a black box warning for all JAK inhibitors (https://www.fda.gov/media/151936) regarding their increased risk for malignancies and thrombosis, mainly based on a tofacitinib trial in patients with rheumatoid arthritis [3]. Also, the use of bDMARDs is often discouraged in patients with established malignancies, mainly owing to the exclusion of such patients in pivotal clinical trials and, hence, the lack of evidence for use in such patients. In addition, patients with autoimmune disease, such as psoriasis and rheumatoid arthritis, were shown to have higher malignancy risks [4]. Thus, it is timely to reassess the carcinogenicity and antineoplastic properties of csDMARDs.

The long-term use of some csDMARDs is considered to increase the risk of malignancy [5–10]. However, evidence suggests that some csDMARDs have antineoplastic effects and may be used to treat malignancies. The concept that chronic inflammation is associated with carcinogenesis has been well established [11], and the antiinflammatory effects of csDMARDs may be contributory to their antineoplastic properties. Although the exact antineoplastic mechanisms of csDMARDs remain unknown, some csDMARDs, such as CQ, HCQ, CsA, etc., have already been utilized in cancer management for a long time. This review focuses on csDMARDs reported to have antineoplastic potential in their commonly used dosages as DMARDs.

METHODS

A literature search of the PubMed database was conducted using the keywords (Drug name [MeSH Terms]) AND (Neoplasm [MeSH Terms]), from inception to 20 September 2021. Citation lists of selected articles were used to identify other relevant articles. Afterwards, a two-step search was conducted. First, we identified types of cancer related to a specific csDMARD, and then we used the drug names and the cancer
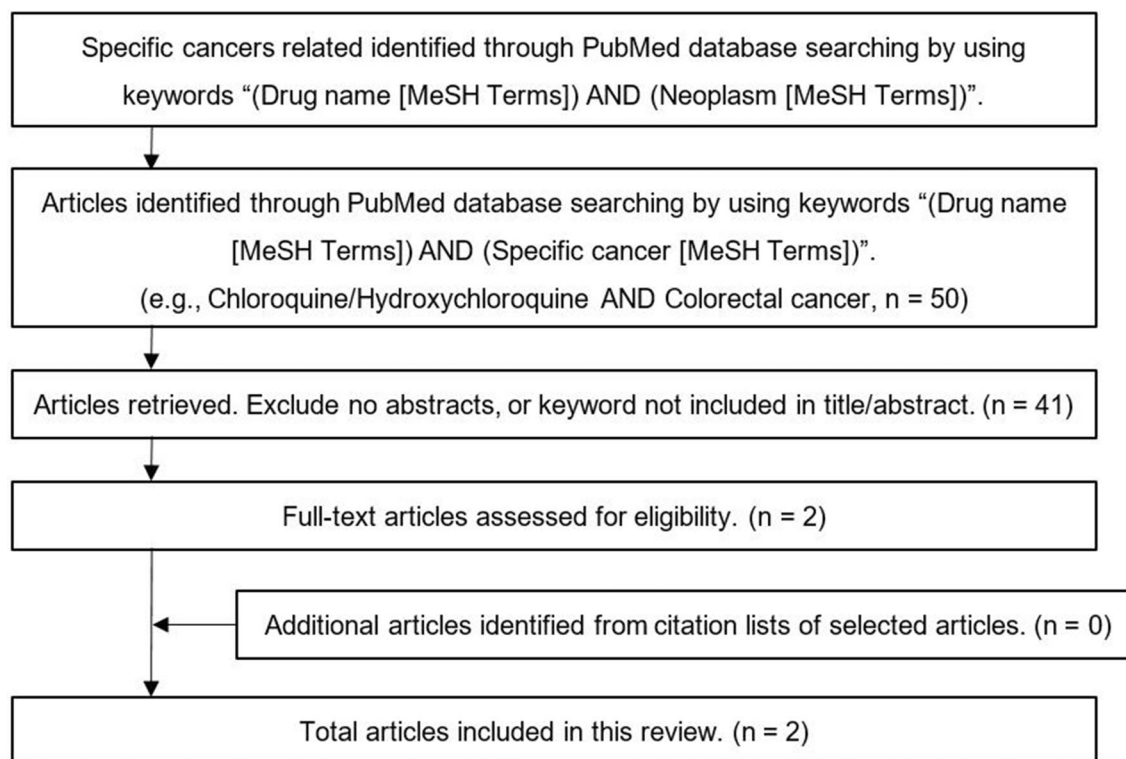
Fig. 1 Flow chart of the article searching strategy. A two-step search was conducted as follows: Step 1: (Drug name [MeSH Terms]) AND (Neoplasm [MeSH Terms]) → identify the specific cancer. Step 2: (Drug name [MeSH Terms]) AND (Specific cancer [MeSH Terms])

types we identified as keywords to search for more relevant articles. Articles were screened and selected, and then the quality of the studies was assessed by Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence according to their study designs [12]. A detailed flow chart of the article searching strategy is shown in Fig. 1. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

DMARDs have been proven to have efficacy in different malignancies through a variety of mechanisms (Tables 1 and 2). For patients with immune-based diseases and malignancies, some

oral DMARDs could be the treatment of choice owing to their antineoplastic activity.

Chloroquine and Hydroxychloroquine

CQ and HCQ are 4-aminoquinolines that have been used for malaria treatment. As csDMARDs, they are also indicated for rheumatoid arthritis and systemic lupus erythematosus. Cancer cell survival was found related to autophagy [13, 14], which clears damaged cellular debris delivered to lysosomes. HCQ inhibits autophagy by blocking the fusion of the autophagosome to the lysosome, which may lead to an antineoplastic effect [13, 14].

Reviews
In a nationwide population-based cohort study, patients with autoimmune diseases were enrolled and patient data were collected from Taiwan National Health Insurance Database. After

Table 1 Mechanisms regarding antineoplastic activities of DMARDs

Medication	Proposed antineoplastic mechanism	Preclinical study	Malignancies with clinical study
csDMARDs	1. Antiinflammatory effect		
CQ/HCQ	1. Autophagy inhibition	V	Glioma, melanoma, multiple myeloma, lung cancer, pancreatic cancer, solid organ tumor, sarcoma
	2. Inhibition of the TLR9/ nuclear factor kappa B (NF-κB) signaling pathway		
	3. Inhibition of CXCL12/CXCR4 signaling		
	4. Interference with the p53 pathway,		
	5. Modulation of tumor microenvironment		
CsA	1. Modulation of MDR expression and membrane P-glycoprotein (P-gp)	V	Non-small cell lung cancer, chronic myeloid leukemia
	2. Inhibition of cytochrome P-450 enzyme system		
	3. Activation of caspase-3 and caspase-9		
	4. Inhibition of nuclear factor-κB (NF-κB) activation		
	5. Inhibition of PI3 kinase–AKT1 signaling pathway		
	6. Inhibition of Wnt/calcineurin/NF-AT pathway		
Leflunomide	1. Inhibition of the mitochondrial enzyme dihydroorotate dehydrogenase	V	Multiple myeloma
	2. Inhibition of the tyrosine kinase activity of platelet-derived growth factor receptors (PDGFR) and EGFR		
MTX	1. Inhibition of dihydrofolate reductase (DHFR)	V	Breast cancer, head and neck cancer, leukemia
MMF/MPA	1. Regulation of the de novo purine synthesis pathway via inhibiting the inosine monophosphate dehydrogenase (IMPDH)	V	Pancreatic cancer, lymphoma, multiple myeloma
	2. Suppression of the function of VEGF		
SSZ	1. Inhibition of the xc⁻ cystine transporter	V	Gastric cancer, glioma, non-small cell lung cancer, urogenital cancer
	2. Inhibition of matrix metalloproteinase-related genes		
	3. Increase in accumulation of intracellular ROS		
	4. Inhibition of nuclear factor-κB (NF-κB) activation		

Table 1 continued

Medication	Proposed antineoplastic mechanism	Preclinical study	Malignancies with clinical study
Thiopurines	1. Antiinflammatory effect		Colorectal cancer, multiple myeloma

csDMARDs conventional synthetic disease-modifying antirheumatic drugs, *CQ* chloroquine, *CsA* cyclosporine A, *MMF* mycophenolate mofetil, *MPA* mycophenolic acid, *MTX* methotrexate, *SSZ* sulfasalazine

propensity score matching, HCQ use did not increase the cancer risk in Taiwanese patients with autoimmune diseases [15].

Manic et al. and Verbaanderd et al. have carefully reviewed the efficacy of CQ and HCQ as antineoplastic agents. Beneficial effects of CQ or HCQ monotherapy administration were noted in a range of cancer types in in vivo studies. CQ or HCQ in combination with various anticancer agents, including chemotherapeutic drugs, tyrosine kinase inhibitors, various monoclonal antibodies, hormone therapies, and radiotherapy, also showed satisfying results in in vitro models. Recently, clinical trials investigating the response of CQ or HCQ in combination with other anticancer agents have been completed or are ongoing. Promising outcomes have been observed in patients with glioma and multiple myeloma treated with CQ in addition to other anticancer treatment. In patients with solid organ tumors, glioblastoma, lung cancer, multiple myeloma, pancreatic cancer, or sarcoma, combination therapies of HCQ and anticancer agents have also shown good results. The antineoplastic mechanism of CQ and HCQ may result from (1) autophagy inhibition, (2) inhibition of the TLR9/ nuclear factor kappa B (NF-κB) signaling pathway, (3) inhibition of CXCL12/CXCR4 signaling, (4) interference with the p53 pathway, and (5) modulation of tumor microenvironment. In short, CQ and HCQ improve the therapeutic effects of chemo-, radio-, and immunotherapeutic antineoplastic regimens in many different cancer types [16, 17].

Colorectal Cancer
Preclinical models showed that HCQ enhances the antineoplastic activity of vorinostat (VOR) in colorectal cancer (CRC) cells [18]. A cohort study of HCQ and VOR in patients with refractory metastatic CRC reported a survival outcome comparable to other treatment in metastatic CRC [19].

Glioma
Studies showed that adding CQ to conventional treatment may be beneficial for patients with glioblastoma multiforme (GBM). Improved survival outcomes have been observed in patients with adjuvant CQ treatment compared with controls [20, 21]. Nonetheless, a phase I/II clinical trial showed HCQ combined with radiotherapy (RT) and temozolomide (TMZ) in patients with GBM achieved no significant improvement in overall survival (OS), which might be related to inadequate autophagy inhibition [22].

Melanoma
Autophagy is found to be associated with melanoma cell survival. A preclinical study showed that autophagy inhibition with HCQ significantly augments TMZ cytotoxicity in melanoma cells [23]. A phase I trial reported that, among 29 evaluable patients with advanced solid tumors and melanoma, 3 had partial remission (PR) and 8 had stable disease (SD) on HCQ and dose-intense TMZ [24].

A preclinical study reported that HCQ has a synergistic antineoplastic effect when combined with the mTOR inhibitor temsirolimus (TEM) in melanoma cells [25]. A phase I trial demonstrated that, among 21 evaluable patients with advanced solid tumors and melanoma, 14 had SD on HCQ and TEM [26].

Table 2 Clinical studies regarding antineoplastic activity of DMARDs

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
CQ/HCQ	Brain metastasis	RCT	Level 2	73 (CQ + whole-brain RT/whole-brain RT 39/34)	150 mg/day	Treatment with CQ increased PFS of brain metastases (RR 0.31,95% CI 0.1–0.9, $P = 0.046$)	Rojas-Puentes, 2013 [140]
		Cohort study	Level 3	20	250 mg/day	Among 16 evaluable patients with brain metastasis treated with CQ and whole-brain RT, 2 had CR, 13 had PR, and one had SD	Eldredge, 2013 [141]
	Colorectal cancer	Cohort study	Level 3	20	600 mg/day	In 19 evaluable patients with metastatic CRC, a median PFS of 2.8 months and a median OS of 6.7 months, treated with vorinostat and HCQ	Patel, 2016 [19]
	Glioma	RCT	Level 2	18 (CQ/ctrl 9/9)	150 mg/day	Significantly longer survival in patients with additional CQ treatment than in controls (33 ± 5 versus 11 ± 2 months; $P = 0.0002$)	Briceño, 2003 [142]
		RCT	Level 2	30 (CQ/ctrl 15/15)	150 mg/day	Adding CQ to conventional treatment improved median survival postoperatively in patients with GBM compared with controls (24 versus 11 months)	Sotelo, 2006 [20]
		Case–control study	Level 4	123 (CQ/ctrl 41/82)	150 mg/day	Improved survival in patients with GBM treated with adjuvant CQ (mean survival 25 ± 3.4 versus 11.4 ± 1.3 months; $P = 0.000$; OR 0.4, 95% CI 0.26–0.6)	Briceño, 2007 [21]
		Case series	Level 4	92 (phase I/II 16/76)	200–800 mg/day	No significant improvement in overall survival was noted at the maximal tolerated dose of HCQ 600 mg/day	Rosenfeld, 2014 [22]
	Melanoma	Case series	Level 4	40	200–1200 mg/day	Among 29 evaluable patients with advanced solid tumors and melanoma, 3 had PR and 8 had SD on HCQ and dose-intense temozolomide	Rangwala, 2014 [24]
		Case series	Level 4	39	200–1200 mg/day	Among 21 evaluable patients with advanced solid tumors and melanoma, 14 had SD on HCQ and temsirolimus	Rangwala, 2014 [26]
	Multiple myeloma	Case series	Level 4	22	100–1200 mg/day	Among the evaluable patients, three (14%) achieved PR, three (14%) had minor responses, and ten (45%) achieved SD	Vogl, 2014 [30]
	Multiple types of cancer	Cohort study	Level 3	3986 (HCQ/ctrl 1993/1993)	Not mentioned	HCQ did not increase the cancer risk in Taiwanese patients with autoimmune diseases	Mao, 2018 [15]
	Non-small cell lung cancer	Case series	Level 4	27 (HCQ/HCQ + erlotinib 8/19)	400–1000 mg/day	Among 19 patients on HCQ and erlotinib, 1 had PR and 4 had SD	Goldberg, 2012 [31]
		Case series	Level 4	38 (phase Ib/II 8/30)	400 mg/day	ORR of 33% to carboplatin, paclitaxel (and bevacizumab if eligble), and HCQ in 30 evaluable patients with metastatic NSCLC	Malhotra, 2019 [32]
	Pancreatic cancer	Case series	Level 4	20	800 or 1200 mg/day	In patients with previously treated metastatic pancreatic cancer, minimal therapeutic efficacy of HCQ monotherapy was observed	Wolpin, 2014 [35]
		Case series	Level 4	35	200–1200 mg/day	In patients with pancreatic adenocarcinoma, preoperative autophagy inhibition with HCQ plus gemcitabine was safe and effective	Boone, 2015 [143]

Table 2 continued

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
		RCT	Level 2	112 (HCQ + GA/GA 56/56)	1200 mg/day	ORR improvement was observed in the HCQ group (38.2% versus 21.1%; $P = 0.047$); however, OS showed no significant difference	Karasic, 2019 [36]
		RCT	Level 2	64 (34/30 HCQ + GA/GA)	1200 mg/day	HCQ with gemcitabine and nab-paclitaxel led to a better pathologic tumor response in patients with resectable pancreatic cancer ($P = 0.00016$)	Zeh, 2020 [37]
	Renal cell carcinoma	Case series	Level 4	33	800–1200 mg/day	In patients with RCC, 2 (6%) had PR and 20 had SD (61%) on everolimus and HCQ	Haas, 2019 [39]
	Sarcoma	Case series	Level 4	10	400 mg/day	In ten sarcoma patients treated with HCQ and rapamycin, six had PR and three had SD	Chi, 2015 [144]
	Solid organ tumors	Cohort study	Level 3	25	400 mg/day	In patients with metastatic solid tumor on adjuvant rapamycin and HCQ with metronomic chemotherapy, an ORR of 40% and a disease control rate of 84% were observed	Chi, 2015 [44]
		Case series	Level 4	27	400–1000 mg/day	Among 24 evaluable patients with advanced solid tumors treated with HCQ in combination with vorinostat, 1 had PR and 10 had SD	Mahalingam, 2014 [145]
CsA	Colorectal cancer	Case series	Level 4	39	4 mg/kg/day	Among 39 patients with metastatic CRC, 2 had PR and 18 had SD, treated with the combination of oral selumetinib and CsA	Krishnamurthy, 2018 [55]
	Chronic myeloid leukemia	Case series	Level 4	2	250–400 mg/day	CsA enhances the effect of dasatinib in Bcr-Abl + leukemia; combination of dasatinib and CsA led to hematopoietic toxicity in two patients with CML	Gardner, 2014 [52]
	Gastric cancer	Case series	Level 4	24	10 mg/kg/week	Among 24 patients with advanced gastric cancer on oral CsA and paclitaxel, 8 had PR and 11 had SD with an ORR of 33% (95% CI 18–52%)	Kruijtzer, 2003 [61]
	Non-small cell lung cancer	Case series	Level 4	26	10 mg/kg/week	Oral paclitaxel and CsA had an ORR of 26% (95% CI 10–48%) in patients with advanced NSCLC	Kruijtzer, 2002 [62]
Leflunomide	Multiple myeloma	Case series	Level 4	11	20–60 mg/day	In patients with relapsed/refractory multiple myeloma, 9 out of 11 achieved SD on leflunomide	Rosenzweig, 2020 [74]

Table 2 continued

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
MTX	Breast cancer	Case series	Level 4	63	10 mg/week	Among patients with metastatic breast cancer on oral MTX and cyclophosphamide, two had CR, ten had PR (ORR 19.0%, 95% CI 10.2–30.9%), and eight had SD	Colleoni, 2002 [81]
		Case series	Level 4	48	10 mg/week	Among patients with metastatic breast cancer on oral MTX and cyclophosphamide, 1 patient achieved CR, 10 had PR, and 19 had SD	Hussein, 2017 [82]
	Head and neck cancer	Non-RCT	Level 3	123 (oral MTX + RT/IV MTX + RT/RT 48/36/39)	7.5 mg/day for 5 days	Patients with head and neck cancer on oral MTX prior to radiotherapy had better 3-year survival (33% versus 20% versus 10%, $P = 0.04$) and tumor regression	Lustig 1976 [83]
		Cohort study	Level 3	84	15 mg/m^2/week	Among patients with head and neck cancer treated with oral MTX and celecoxib, 9 (11%) patients had PR and 47 (56%) had SD	Harsh, 2020 [84]
	Leukemia	RCT	Level 2	144 (oral/IM 75/39)	20 mg/m^2/week	In children with ALL, oral MTX is as effective as IM MTX	Chessells, 1987 [85]
		Case series	Level 4	10	5–20 mg/week	Among patients with LGL leukemia, five achieved CR and one achieved PR	Loughran, 1994 [90]
		Case series	Level 4	96	150 mg/m^2 every 2 weeks	In children with ALL, low-dose methotrexate/mercaptopurine is effective and safe	Mahoney, 1995 [88]
		RCT	Level 2	164 (IV + oral/oral 80/80)	20 mg/m^2/week	In children with ALL, oral MTX is as effective as oral + IV MTX	Lange, 1996 [86]
		Case series	Level 4	239	100 mg/m^2/week	In children with ALL, divided-dose oral MTX is effective	Winick, 1996 [87]
		Non-RCT	Level 3	233 (MTX + 6-MP/LSA$_2$L$_2$ 135/98)	20 mg/m^2/week	In children with T-lineage or with higher-risk B-lineage ALL, oral MTX and mercaptopurine are effective as a maintenance therapy	Schmiegelow, 2009 [89]
		Case series	Level 4	24	10 mg/m^2/week	In patients with LGL leukemia, long-term single-agent oral MTX leads to longer responses compared with prednisolone	Munir, 2016 [91]
MMF/MPA	Lymphoma	Cohort study	Level 3	13,502 (MMF/ctrl 6751/6751)	Not mentioned	The risk of developing lymphoma and post-transplant lymphoproliferative disease in the MMF group was reduced	Robson, 2005 [97]
	Multiple myeloma	Case series	Level 4	11	1–5 g/day	PR in a patient (9%), SD in four patients (36%), and progressive disease in six patients	Takebe, 2004 [98]
	Pancreatic cancer	Non-RCT	Level 3	18 (MMF/ctrl 12/6)	1 or 2 g/day	In patients with resectable pancreatic cancer, no significant various expression of VEGF was noted in the MMF group	Rodríguez-Pascual, 2013 [99]

Table 2 continued

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
SSZ	Colorectal cancer	Cohort study	Level 3	26 (long-/short-term SSZ 13/13)	Not mentioned	In patients with UC-related cancer, long-term SSZ is suggested to suppress the differentiation and proliferation of CRC cells	Seishima, 2016 [117]
	Gastric cancer	Case series	Level 4	8	8–12 g/day	In eight patients with CD44v$^+$ advanced gastric cancer, 4 patients had reduced cancer cell population in post-SSZ treatment biopsy tissue	Shitara, 2017 [120]
		Case series	Level 4	7	6 g/day	Among seven patients with CD44v$^+$ gastric cancer refractory to cisplatin, one patient achieved SD for more than 4 months on SSZ combined with cisplatin	Shitara, 2017 [121]
	Glioma	Case series	Level 4	10	1.5–6 g/day	No clinical response or unbearable side effects were observed	Robe, 2009 [122]
		Non-RCT	Level 3	24 (sulfasalazine/ctrl 12/12)	1–4 g/day	Temozolomide and SSZ with RT had no antineoplastic activity in postoperative patients with newly diagnosed glioblastoma	Takeuchi, 2014 [123]
	Non-small cell lung cancer	Case series	Level 4	15	1.5–4.5 g/day	Among 15 patients with CD44v$^+$ advanced NSCLC, 4 achieved PR (ORR 26.7%) and 7 achieved SD (46.7%) on SSZ in combination with cisplatin and pemetrexed	Otsubo, 2017 [124]
	Urogenital cancer	Case reports	Level 4	2	Not mentioned	Impressive results were observed in two patients with advanced urogenital cancer treated with SSZ and anticancer therapies	Takayama, 2016 [126]
Thiopurines	Colorectal cancer	Cohort study	Level 3	755	2 mg/kg/day	No significant decrease in the risk of colorectal neoplasia (OR 1.13, 95% CI 0.46–2.77)	Connell, 1994 [146]
		Cohort study	Level 3	98	Not mentioned	No significant decrease in the risk of colorectal neoplasia (RR 1.12, 95% CI 0.26–4.77)	Lashner, 1997 [147]
		Case–control study	Level 4	59 (case/ctrl 26/33)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.68, 95% CI 0.17–2.6)	Tung 2001 [148]
		Cohort study	Level 3	2204	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.86, 95% CI 0.43–1.73)	Fraser, 2002 [149]
		Case–control study	Level 4	204 (case/ctrl 68/136)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (< 5-year use: OR 0.34 95% CI 0.09—1.25; > 5-year use: OR 0.73, 95% CI 0.30–1.78)	Rutter, 2004 [150]
		Cohort study	Level 3	315	Average dose 60.6 ± 19.5 mg/day	No significant decrease in the risk of colorectal neoplasia (HR 1.06, 95% CI 0.59–1.93)	Matula, 2005 [151]
		Cohort study	Level 3	723	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 1.57, 95% CI 0.19–12.4)	Lakatos, 2006 [152]
		Case–control study	Level 4	376 (case/ctrl 188/188)	average dose case/ctrl 1.0/1.3 mg/kg/day	No significant decrease in the risk of colorectal neoplasia (> 1-year use: OR 3.0, 95% CI 0.7–13.6)	Velayos, 2006 [153]
		Cohort study	Level 3	418	Not mentioned	No significant decrease in the risk of colorectal neoplasia (HR 1.0, 95% CI 0.6–1.6)	Gupta, 2007 [154]

Table 2 continued

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
		Case–control study	Level 4	15,441 (case/ctrl 392/15049)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.68, 95% CI 0.35–1.29)	Armstrong, 2010 [155]
		Case–control study	Level 4	48 (case/ctrl 18/30)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.38, 95% CI 0.04–3.72)	Tang, 2010 [156]
		Case–control study	Level 4	551 (case/ctrl 159/392)	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (OR 0.3, 95% CI 0.16–0.56)	Baars, 2011 [157]
		Cohort study	Level 3	2578	At least 50 mg/day	Statically significant decrease in the risk of colorectal neoplasia (OR 0.1, 95% CI 0.01–0.75)	van Schaik, 2011 [158]
		Cohort study	Level 3	1084	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.27, 95% CI 0.02–4.53)	Setshedi, 2011 [159]
		Cohort study	Level 3	19,486	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (HR 0.28, 95% CI 0.1–0.9)	Beaugerie, 2013 [160]
		Cohort study	Level 3	812	AZA 50–250 mg/day, 6-MP 25–150 mg/day	Statically significant decrease in the risk of colorectal neoplasia (OR 0.96, 95% CI 0.94–0.98)	Gómez-García, 2013 [161]
		Cohort study	Level 3	43,969	Not mentioned	No significant decrease in the risk of colorectal neoplasia (HR 1.00, 95% CI 0.61–1.63)	Pasternak, 2013 [162]
		Case–control study	Level 4	200 (case/ctrl 59/141)	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (all: OR 0.28, 95% CI 0.12–0.65; < 2-year use: OR 0.19, 95% CI 0.05–0.70; > 2-year use: OR 0.27, 95% CI 0.09–0.78)	Rubin, 2013 [163]
		Case–control study	Level 4	54 (case/ctrl 27/27)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 1.23, 95% CI 0.35–4.28)	Satchi, 2013 [164]
		Case–control study	Level 4	553 (case/ctrl 183/370)	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (OR 0.31, 95% CI 0.19–0.51)	Nieminen, 2014 [165]
		Case–control study	Level 4	831 (case/ctrl 45/786)	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (OR 0.21, 95% CI 0.06–0.74)	Gordillo, 2015 [166]
		Case–control study	Level 4	3744 (case/ctrl 343/3401)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (RR 0.99, 95% CI 0.75–1.31)	Kopylov, 2015 [167]
		Cohort study	Level 3	434	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.7, 95% CI 0.1–3.3)	Nowacki, 2015 [168]
		Case–control study	Level 4	202 (case/ctrl 29/173)	Not mentioned	Statically significant decrease in the risk of colorectal neoplasia (HR 0.30, 95% CI 0.13–0.70)	Navaneethan, 2016 [169]
		Case–control study	Level 4	430 (case/ctrl 144/286)	Not mentioned	No significant decrease in the risk of colorectal neoplasia (OR 0.762, 95% CI 0.432–1.343)	Carrat, 2017 [170]

Table 2 continued

Medication	Malignancy	Study design	OCEBM Levels of Evidence	Numbers of subject	Dose	Clinical report	Article
	Multiple myeloma	RCT	Level 2	74 (AZA 26)	300 mg/day	In the azathioprine group, six patients achieved remission with a response rate of 23.1%	JAMA, 1975 [135]
		RCT	Level 2	71 (AZA + prednisone 35)	125 mg/m²/day for 7 days	Patients receiving azathioprine–prednisone as a maintenance treatment had similar survival and remission duration compared with those receiving other chemotherapy regimens	Alexanian, 1977 [136]
		RCT	Level 2	270 (PAIV 80)	100 mg/m²/day for 7 days	Among 80 patients receiving PAIV as a maintenance treatment, 42 had improvement or maintenance response. A longer median duration of remission (16.2 months) without significant difference was also noted in PAIV group	Cohen, 1986 [137]

6-MP 6-mercaptopurine, *AZA* azathioprine, *ALL* acute lymphoblastic leukemia, *CI* confidence interval, *CQ* chloroquine, *CR* complete response, *CRC* colorectal cancer, *CsA* cyclosporine A, *ctrl* control, *GBM* glioblastoma multiforme, *HR* hazard ratio, *IM* intramuscular, *IV* intravascular, *LGL* large granular lymphocyte, *MMF* mycophenolate mofetil, *MPA* mycophenolic acid, *MTX* methotrexate, *NSCLC* non-small cell lung cancer, *OR* odds ratio, *ORR* overall response, *PAIV* prednisone, adriamycin, azathioprine, vincristine, *PFS* progression-free survival, *PR* partial response, *RCC* renal cell carcinoma, *RCT* randomized controlled trial, *RR* relative risk, *RT* radiotherapy, *SD* stable disease, *SSZ* sulfasalazine, *UC* ulcerative colitis, *VEGF* vascular endothelial growth factor

Multiple Myeloma

Preclinical studies demonstrate that autophagy inhibition increases the antineoplastic activity of bortezomib in myeloma [27–29]. Therefore, the safety and efficacy of HCQ and bortezomib in patients with MM were studied in a phase I trial. Among 22 evaluable patients, 3 (14%) achieved PR, 3 (14%) had minor responses, and 10 (45%) achieved SD. The treatment was well tolerated and suggested to be a potential treatment option for patients with MM [30].

Non-small Cell Lung Cancer

A phase I trial showed an ORR of 5% (95% CI 1–25%) to HCQ and erlotinib in advanced non-small cell lung cancer (NSCLC) patients. In 19 patients on HCQ and erlotinib, 1 had PR for 20 months, which was longer than expected, and 4 had SD [31].

A phase Ib/II trial showed a higher objective response rate (ORR) was achieved by HCQ in combination with chemotherapy compared to chemotherapy alone. Furthermore, an even better result was reported in 9 patients with KRAS-positive NSCLC [32].

Pancreatic Cancer

Autophagy is related to pancreatic cancer growth and inhibitors of autophagy, such as CQ, may be helpful in pancreatic cancer treatment [33, 34]. HCQ monotherapy showed minimal therapeutic efficacy in patients with metastatic pancreatic cancer [35]. However, combined with gemcitabine and nab-paclitaxel (GA), HCQ improved the ORR in patients with advanced pancreatic cancer [36]. In addition, HCQ with GA leads to a better pathologic tumor response in patients with resectable pancreatic cancers [37]. Although the use of GA with HCQ is not routine practice, it may be beneficial as a neoadjuvant therapy for patients with locally advanced pancreatic cancer.

Renal Cell Carcinoma

A previous study showed mTOR inhibitor combined with HCQ causes synergistic cell death in renal cell carcinoma (RCC) cells [38]. In a phase I/II trial, everolimus, an mTOR inhibitor, and HCQ were administered to

patients with previously treated RCC. In 33 patients, two (6%) had PR, and 20 had SD (61%). Combined with everolimus, HCQ is safe and effective in patients with RCC [39].

Solid Organ Tumors

Preclinical studies showed that autophagy is related to the growth of solid organ tumors, such as bladder cancer [40, 41]. CQ and HCQ treatment leads to bladder cancer cell apoptosis [42] and growth suppression through the downregulation of matrix metalloproteinase-2 (MMP-2) by inhibiting autophagy [43].

In a small patient cohort study, HCQ and rapamycin were added to metronomic chemotherapy for patients with refractory metastatic solid tumors. In 24 evaluable patients with advanced solid tumors treated with HCQ in combination with vorinostat, one achieved PR and ten achieved SD [44].

Cyclosporine A

Cyclosporine A (CsA) is used for rheumatoid arthritis, psoriasis, systemic lupus erythematosus (SLE), severe atopic dermatitis, polymyositis, and dermatomyositis. It also has efficacy in preventing graft versus host disease and rejection in human organ transplantation. CsA has been reported to induce cancer progression and promote cancer cell growth [45], but recently antineoplastic activities of CsA were observed. CsA binds to cyclophilin, forming a complex that inhibits calcineurin and blocks the dephosphorylation of nuclear factor of activated T cells (NF-AT). Hence, the gene transcription of IL-2, IL-3, IFN-γ, and other factors are interfered, causing an immunosuppressive effect.

In vitro and in vivo studies have shown CsA may enhance the antineoplastic effect of chemotherapeutic agents and target therapeutic agents in different multidrug resistance malignancies. The antineoplastic property of CsA may act through (1) modulation of MDR expression and the membrane P-glycoprotein (P-gp), (2) inhibition of the cytochrome P-450 enzyme system [46], (3) activation of caspase-3 and caspase-9 [47–49], (4) inhibition of the NF-

κB activation [50], (5) inhibition of the PI3 kinase-AKT1 signaling pathway [47] or (6) inhibition of the Wnt/calcineurin/NF-AT pathway [51–54].

Colorectal Cancer

Selumetinib is an oral MEK inhibitor, and it has been utilized as a treatment for patients with KRAS mutant CRC. However, limited clinical activity was observed and the resistance was found to be associated with the Wnt signaling pathway [54]. CsA, a Wnt/calcineurin/NF-AT signaling pathway modulator [51], is proposed to reverse the resistance of selumetinib in patients with CRC. To examine the hypothesis, a phase I/Ib trial investigated the efficacy of the combination of oral selumetinib and CsA in metastatic CRC patients. The combination of oral selumetinib and CsA was effective and well-tolerated. Totally, 39 patients were enrolled with two PR and 18 SD observed [55].

Chronic Myeloid Leukemia

CsA also plays a role in target therapy for Bcr-Abl[+] chronic myeloid leukemia (CML). Dasatinib, a Bcr-Abl kinase inhibitor, is commonly used to treat Bcr-Abl[+] CML. Wnt/Calcineurin/NF-AT signaling pathway, which is critical for the survival of Bcr-Abl^{+} leukemia cells, was inhibited by CsA. Targeting the pathway, CsA enhanced the sensitivity to Bcr-Abl kinase inhibitors in Bcr-Abl^{+} leukemia cells [51, 52]. A phase Ib trial demonstrated two CML patients treated with dasatinib and cyclosporine. Enhanced serum concentrations of dasatinib in patients were reported. However, more hematopoietic toxicity than expected was noted. Although the combination may be effective, the toxicity limits its use in clinical practice [52].

Gastric Cancer

Paclitaxel, a chemotherapeutic agent commonly used for advanced gastric cancer, is often administered by intravenous injection. Although oral paclitaxel is more convenient for long-term treatment schedules, low oral bioavailability due to drug efflux by the membrane P-gp in the gastrointestinal tract was

observed [56, 57]. Co-administration of oral CsA, acting as a P-gp inhibitor, significantly increased the bioavailability of oral paclitaxel [58–60]. A phase II trial enrolled 24 patients with advanced gastric cancer receiving the treatment of oral CsA and paclitaxel. Eight patients with PR, 11 with SD and an ORR of 33% (95% CI 18–52%) were observed [61]. The ORR was comparable with patients receiving intravenous paclitaxel therapy. Oral CsA and paclitaxel is an effective regimen in patients with advanced gastric cancer.

Non-small Cell Lung Cancer

A phase II trial showed that oral CsA and paclitaxel have efficacy in advanced NSCLC. Twenty-six patients received oral CsA and paclitaxel, and six patients achieved PR. The ORR was of the 23 assessable patients was 26% (95% CI 10–48%) with a median duration of 16 weeks. Furthermore, stabilization of the disease was noted in eight patients (35% of the assessable population) with a median duration of 17 weeks. The efficacy of oral CsA and paclitaxel was better than that of other drugs used in a single-agent setting. The safety profile of the treatment was also acceptable [62].

Leflunomide

Leflunomide has been approved for the treatment of patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). Leflunomide is converted to its active metabolite, teriflunomide, in the intestine and in the plasma. Leflunomide influences the de novo pyrimidine synthesis pathway via inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), leading to the arrest of cell growth [63]. Leflunomide also inhibits the tyrosine kinase activity of platelet-derived growth factor receptors (PDGFR) and epidermal growth factor receptor (EGFR), which are commonly expressed in tumor cells [63]. According to some preclinical studies, leflunomide showed antineoplastic activities in several malignancies, including prostate, breast, bladder, multiple myeloma, leukemia, and lymphoma [64–73].

Multiple Myeloma

A phase I trial demonstrated that patients with relapsed/refractory multiple myeloma (MM) were successfully treated by single-agent leflunomide. Twelve patients were enrolled in this study; one patient was not evaluable for response, and 9 out of 11 patients achieved SD on leflunomide. The safety profile showed that leflunomide is well tolerated up to a dosage of 60 mg/day with minimal toxicity [74].

Methotrexate

Methotrexate (MTX) is the first-line treatment for RA, PsA, and other forms of inflammatory arthritis. It is also effective for atopic dermatitis, dermatomyositis, SLE, and other autoimmune diseases. MTX has been known to suppress the inflammatory and immune response through an adenosine-mediated effect by inhibiting aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase [75, 76].

However, the use of MTX has been found to be associated with increased incidence of certain cancers, including melanoma, non-Hodgkin's lymphoma, and lung cancer [77]. Despite the fact that MTX may be related to an elevated risk of cancer, antineoplastic effects of MTX have also been reported. Some studies suggest that MTX does not increase the risk of either noncutaneous or cutaneous malignancies [78, 79] or even might lower the risk of new-onset cancer [80]. For instance, high dose of MTX has been used for the treatment of malignancies, such as acute leukemia. Evidence showed that MTX blocks dihydrofolate reductase (DHFR), which converts dihydrofolate to tetrahydrofolate (THF), and results in the inhibition of cell proliferation [75, 76]. However, the dose of MTX used in treating cancer may be much higher than the dose used as a DMARD. Therefore, in our article, high-dose MTX ($\geq 500\,\mathrm{mg/m^2}$) use is not discussed.

Breast Cancer

A clinical study showed a good outcome in treating patients with metastatic breast cancer with a combination of low-dose oral MTX and cyclophosphamide. Among 63 evaluable

patients, 2 patients achieved complete response (CR), 10 achieved PR (ORR 19.0%, 95% CI 10.2–30.9%), and 8 had SD [overall clinical benefit (CR + PR + SD > 24 weeks) = 31.7%, 95% CI 20.6–44.7%] [81]. A reduction in serum vascular endothelial growth factor (VEGF) levels was also noted and suggested to be related to the antineoplastic effect of this treatment [81].

Another phase II trial treating patients with metastatic breast cancer with metronomic chemotherapy in the form of low-dose oral MTX and cyclophosphamide showed similar results. Among 48 patients with metastatic breast cancer, 1 patient achieved CR and 10 had PR, while 19 patients had SD [82]. As a result, the combination of oral MTX and cyclophosphamide may be beneficial for patients with metastatic breast cancer.

Head and Neck Cancer

A clinical study showed that patients with head and neck cancer had better 3-year-survival (33% versus 20% versus 10%, $P = 0.04$) and tumor regression treated with oral MTX prior to RT compared with intravenous MTX prior to RT or RT alone [83].

A single-arm retrospective observational study included 84 patients with locally advanced, recurrent, and metastatic head and neck cancer treated with oral metronomic chemotherapy. Oral MTX and celecoxib were administered, and 9 (11%) patients had PR and 47 (56%) had SD [84]. Minimal toxicity and symptomatic relief were observed. Oral MTX and celecoxib may be effective and well tolerated in patients with head and neck cancer [84].

Leukemia

While parenteral administration of MTX, including intravenous and intrathecal, has long been used as treatment of leukemia, oral MTX was also utilized as a regimen of the consolidation therapy in children with lower-risk acute lymphoblastic leukemia (ALL). Evidence shows that it is as effective as parenteral MTX [85–88] and can be administered safely on an outpatient basis. Furthermore, the combination of oral MTX and mercaptopurine also showed benefits

as a maintenance therapy in children with T-lineage or with higher-risk B-lineage ALL [89].

Oral MTX is also an effective treatment for patients with large granular lymphocyte (LGL) leukemia [90]. Long-term single-agent oral MTX leads to longer responses compared with prednisolone and has minimal toxicity [91].

Mycophenolate Mofetil and Mycophenolic Acid

Mycophenolate mofetil (MMF), a semisynthetic derivative of mycophenolic acid (MPA), regulates the de novo purine synthesis pathway via inhibiting the inosine monophosphate dehydrogenase (IMPDH). The de novo pathway is the main pathway of T- and B-lymphocyte purine synthesis [92]. Therefore, MMF and MPA have been known to inhibit the activities of T and B lymphocytes and lead to suppression of the immune system. Because of the immunosuppression effect, MMF has been used in patients with solid organ transplant for refractory rejection. MMF is also indicated for RA, inflammatory bowel disease (IBD), lupus erythematosus, pemphigus, and some other dermatologic disorders. In addition to their immunosuppression effect, MMF and MPA have been reported to be able to inhibit cancer cell proliferation and induce apoptosis in various solid organ tumors and hematological malignancies [93–96].

Lymphoma

A prospective observational cohort study investigated the association of long-term MMF use with the risk of malignancy in patients with renal transplant. Evidence shows that the risk of developing lymphoma and post-transplant lymphoproliferative disease in the MMF group was reduced compared with the non-MMF group. Additionally, a trend toward a lower risk of malignancy and a significant increase in time to malignancy were also reported [97].

Multiple Myeloma

In a phase I trial, 12 patients with progressive MM were on oral MMF twice daily up to a maximum dose of 5 g/day for 4 weeks. Oral

allopurinol 300 mg twice daily was also administered to inhibit the guanine salvage pathway. Among the 11 evaluable study patients, PR in 1 patient (9%), SD in 4 patients (36%), and progressive disease in 6 patients were reported. A significant positive correlation between MPA levels and a decrease in dGTP levels ($P = 0.0001$) was noted. The intracellular dGTP level had a statistically significant reduction in the PR/stable disease group compared with the progressive disease group [98]. Thus, the dGTP level may be useful as a biomarker to evaluate the efficacy of MMF in patients with MM.

Pancreatic Cancer

A preclinical and clinical study was performed to investigate the effects of MPA in pancreatic cancer. Growth inhibition and suppression were demonstrated in exposure of pancreatic cancer cells to MMF in vivo [99]. Then, 12 patients with resectable pancreatic cancer were treated with MMF (1 g/day in 6 patients and 2 g/day in the other 6) from 5 to 15 days prior to surgical resection. However, in the resected specimens, no significant various expression of VEGF was noted in the MMF-treated patients compared with the nontreated control patients [99].

Sulfasalazine

Sulfasalazine (SSZ) is an antiinflammatory drug indicated for patients with IBD, including ulcerative colitis (UC) and Crohn's disease (CD), or rheumatoid arthritis. SSZ and its metabolites (sulfapyridine and 5-aminosalicylic acid) suppress lymphocyte activities and inhibit cytokine release. Preclinical studies showed that SSZ has an antineoplastic effect on lymphoma [100], breast cancer [101–105], colorectal cancer [106], gastric cancer [107], glioma [108–110], lung cancer [111], and prostate cancer. The mechanisms accounting for the antineoplastic effect of SSZ may include (a) inhibition of xc− cystine transporter [100, 110–114], (b) inhibition of matrix metalloproteinase-related genes [102], (c) increasing the accumulation of intracellular reactive oxygen species (ROS) [102], and (d) inhibition of NF-κB activation [108]. However, the actual pharmacological effects of SSZ remain unclear.

Colorectal Cancer

A significantly higher risk of CRC was observed in patients with inflammatory bowel diseases (IBD), including UC and CD [115, 116]. The increased risk of carcinogenesis may be related to the chronic inflammation in the gastrointestinal tract. A retrospective review classified 26 patients with UC-related cancer into long-term (LT) (≥ 5 years) and short-term (ST) (< 5 years) SSZ treatment groups. Preferable immunohistochemical and pathological results were observed in the LT group. In conclusion, long-term SSZ is suggested to suppress the differentiation and proliferation of CRC cells [117].

Gastric Cancer

The expression of splice-variant isoforms of CD44 (CD44v) has been found in solid tumors, including some gastric cancer cell lines, presenting the characteristic of cancer stem cells [118]. CD44v interacts with xCT, a subunit of the xc− cystine transporter, and results in an increase of cystine uptake and enhancement of GSH synthesis. As a result, CD44v-positive cancer cells have properties of cancer stem cells and are resistant to ROS [118, 119]. SSZ, targeting the xc− cystine transporter, is suggested to be an effective treatment for CD44v+ gastric cancer.

A maximum tolerated dose of 12 g/day of SSZ in patients with advanced gastric cancer was confirmed by a dose-escalation study. Furthermore, among eight patients with CD44v+ advanced gastric cancer, four patients had reduced cancer cell population in the post-treatment biopsy tissues after SSZ treatment [120]. Another phase I trial evaluated the efficacy of SSZ combined with cisplatin in patients with CD44v+ advanced gastric cancer refractory to cisplatin. Among seven patients enrolled in the study, one patient achieved SD for more than 4 months [121].

Glioma

Preclinical studies showed a strong antineoplastic activity of SSZ in malignant glioma cells. Therefore, a phase I/II trial was conducted investigating sulfasalazine for recurrent WHO grade 3 and 4 astrocytic gliomas in adults. However, no clinical response or unbearable side effects were observed among the ten patients enrolled in the study [122].

Another clinical study reported that temozolomide and SSZ with radiation therapy have no antineoplastic activity in postoperative patients with newly diagnosed glioblastoma. Progression-free survival (PFS) and OS did not differ between the SSZ and control group. Seizure-free survival was longer in the SSZ group, but no significant difference was noted compared with the control group [123]. Although antineoplastic activities of SSZ were noted in preclinical studies, further studies are needed to prove its benefit in patients with glioblastoma.

Non-small Cell Lung Cancer

A phase I trial administered SSZ in combination with cisplatin and pemetrexed in patients with CD44v$^+$ advanced NSCLC. Among 15 patients enrolled, 4 of them achieved PR (ORR 26.7%) and 7 achieved SD (46.7%). In addition, an 11.7-month median PFS longer than that of patients treated with cisplatin–pemetrexed alone in previous studies was also observed [124].

Urogenital Cancer

Preclinical studies showed that SSZ has antineoplastic effects against prostate cancer due to the inhibition of the xc$^-$ cystine transporter[113, 114, 125]. Case reports have demonstrated that SSZ has clinical benefit in patients with advanced urogenital cancer. Two patients, one with metastatic urinary bladder cancer and the other with castration-resistant prostate cancer, are both diagnosed with RA and receiving SSZ. Immunostaining prior to SSZ treatment showed CD44v9$^+$ cells in both tumors. Despite the poor prognosis of metastatic urinary bladder cancer, the patient achieved CR after a series of chemotherapy, RT, and surgeries, and no CD44v9$^+$ cells were noted in the metastatic lymph nodes or brain metastatic tumor. The other patient with castration-resistant prostate cancer had poor response to chemotherapy. However, during regular carboplatin chemotherapy, significant PSA decrease was observed following the initiation of SSZ in just 2 weeks. According to the impressive results in these two patients, SSZ was suggested to be able to sensitize advanced urogenital cancer to chemotherapy and RT [126].

Thiopurines (Azathioprine/6-Mercaptopurine/ 6-Thioguanine)

Thiopurines, including azathioprine (AZA) and its analog, 6-mercaptopurine (6-MP), are purine antimetabolites. They act through their major metabolite, 6-thioguanine (6-TG), which suppresses immune response in human by interfering with purine nucleic acid metabolism. Owing to the immunosuppressive properties of AZA/6-MP, they are commonly used to treat IBD, including UC and CD. AZA/6-MP also brings benefit in maintaining renal allografts [127, 128]. While long-term use of thiopurines may have potential carcinogenicity [129] and increase the risk of lymphoma [130], anticancer effects of thiopurines have also been reported lately. Also, the malignancy risk of azathioprine was mainly observed in patients with IBD and transplantation. The malignancy risk in patients with atopic dermatitis has been questioned [131].

Colorectal Cancer

The relationship between colorectal dysplasia and thiopurines in patients with IBD is still not clarified. Thiopurines are presumed to decrease the incidence of inflammation-related colorectal dysplasia because of their antiinflammatory effects. Gong et al. have carefully reviewed the antineoplastic effects of thiopurines (AZA/6-MP) against colorectal neoplasia in patients with IBD. Nine case–control and ten cohort studies were selected. Statistically, thiopurines significantly decreased the incidence of colorectal neoplasm in patients with IBD [summary relative risk (RR) 0.71, 95% CI 0.54–0.94, $P = 0.017$]. A tendency to reduce advanced

neoplasia was also noticed [132]. However, Jess et al. came to a different conclusion in their meta-analysis. Reviewing seven cohort studies and eight case–control studies, no significant decrease in the risk of colorectal neoplasia in patients with IBD on thiopurine treatment was observed [pooled odds ratios (OR) = 0.87, 95% CI 0.71–1.06] [133]. Because of the conflicting results of previous researches, another meta-analysis was performed by Zhu et al. to evaluate the protective effects of thiopurines. Eleven cohort and 16 case–control studies were included. The use of thiopurines reduced the risk of colorectal neoplasia both in case–control (OR 0.49, 95% CI 0.34–0.70) and cohort studies (RR 0.96, 95% CI 0.94–0.98). A protective effect of thiopurines against advanced neoplasia and colorectal cancer was also reported. The results indicated that thiopurines have a chemopreventive effect on colorectal neoplasms in patients with IBD [134]. Although some studies have shown a tendency toward a protective effect of thiopurines, the exact efficacy is still not well established and further investigations are suggested.

Multiple Myeloma

Previous research has suggested that AZA, an immunosuppressive agent, may have antitumor activity in the immune system . Thus, AZA was chosen as one of the regimens to treat MM in several clinical trials. A randomized controlled study demonstrated that 23.1% of patients with MM on AZA as a primary agent (6 out of 26) achieved remission. Though the response rate of AZA was significantly lower than that of melphalan and chlorambucil (59.3% and 30.0% respectively, $P = 0.046$), some effects of AZA against MM were still observed [135]. In addition, patients receiving AZA combined with other regimens as a maintenance treatment had similar outcomes compared with those receiving other chemotherapy regimens [136, 137].

DISCUSSION

In this review, we summarize the antineoplastic activity, including possible mechanisms and efficacy, of csDMARDs against different malignancies. The antineoplastic mechanisms of csDMARDs are often distinct from their immunomodulatory pathway. A synopsis of mechanisms regarding antineoplastic activities is presented in Table 1. Included studies and evidence level based on Oxford Centre for EBM (OCEBM) are summarized in Table 2.

Nowadays, the role of csDMARDs in the treatment of immune-mediated inflammatory diseases has been gradually replaced by bDMARDs. However, csDMARDs still constitute the cornerstone in the treatment of these diseases. In addition to their antiinflammatory effects, many DMARDs, especially CQ/HCQ and MTX, have established antineoplastic effects. Although the antineoplastic activity of csDMARDs is based on preclinical or small-scale controlled studies in most cases, the potential to improve the outcome of cancer treatment deserves further investigation. Furthermore, csDMARDs combined with chemotherapy or target therapy may be beneficial in patients with cancer with multiple drug resistance to chemotherapeutic agents. The side effect of increased malignancy risk was the least acceptable to those patients who are receiving treatments for autoimmune disease [138, 139]. Therefore, knowing that csDMARDs have antineoplastic potential may improve drug adherence in these patients. Besides, knowledge of the antineoplastic potential of csDMARDs may guide physicians in the choice of csDMARDs for patients with established malignancies.

Limitations

Currently, the antineoplastic activity of csDMARDs is mostly observed in preclinical or small-scale controlled studies. Further studies are still needed to draw conclusions because the mechanism, efficacy, and safety of most csDMARDs used in treating patients with cancer are still inadequately studied.

CONCLUSIONS

Although biologics have been increasingly used for the treatment of inflammatory diseases, their risk of malignancies is still not fully

assessed. In contrast, the antineoplastic activity of csDMARDs has been reported in preclinical researches, case series, case–control studies, cohort studies, and randomized clinical trials. For patients with coexisting immune-based diseases and malignancy, csDMARDs could be the treatment of choice in certain cases . Nonetheless, the evidence supporting the use of csDMARDs to treat cancer remains limited, and further studies are encouraged.

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