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Recent clinical trials and optical control as a potential strategy to develop microtubule-targeting drugs in colorectal cancer management

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Abstract

Colorectal cancer (CRC) has remained the second and the third leading cause of cancer-related death worldwide and in the United States, respectively. Although significant improvement in overall survival has been achieved, death in adult populations under the age of 55 appears to have increased in the past decades. Although new classes of therapeutic strategies such as immunotherapy have emerged, their application is very limited in CRC so far. Microtubule (MT) inhibitors such as taxanes, are not generally successful in CRC. There may be some way to make MT inhibitors work effectively in CRC. One potential advantage that we can take to treat CRC may be the combination of optical techniques coupled to an endoscope or other fiber optics-based devices. A combination of optical devices and photo-activatable drugs may allow us to locally target advanced CRC cells with highly potent MT-targeting drugs. In this Editorial review, we would like to discuss the potential of optogenetic approaches in CRC management.

Key Words: Colorectal cancer; Chemotherapy; Microtubule; Combretastatin; Photopharmacology

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Core Tip: This review article proposes a potentially new approach to utilize photo-switchable microtubule (MT)-targeting drugs in colorectal cancer (CRC). First, we will start the introduction of CRC and current therapy as well as some updates in 2023. Then, we list a popular MT-targeting drug family, taxanes in CRC. As many readers may be aware, taxanes are not really effective in CRC for some reason. Here, we would like to shed light on optically controllable MT-targeting drugs as potential new drug candidates in CRC management.

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INTRODUCTION

Currently, colorectal cancer (CRC) is the third leading cause of cancer-associated death in the United States and the second worldwide. Based on the most updated CA report, 153020 estimated new cases of CRC in the United States this year (2023)[1]. The overall CRC mortality decreased from 29.2 per 100000 (1970) to 12.6 per 100000 (2020). In addition, mortality decline has surpassed incidence, because improved treatments extended patient survival. Although the age-standardized incidence of CRC has decreased by nearly 50% in 2019, compared to the incidence in 1985, a rapid increase of advanced CRC in the range of 20-50 years old is alarming, because this is the socially very active age group that also contributes to growing the next generation by having families. As widely introduced to the public earlier this year by news media[2,3], this trend gets the attention of the general public. Thus, although the diagnosis and treatments have been significantly developed during the past two decades, it is still very important to us to further develop more effective treatments for CRC, with a primary focus on advanced CRC. As the early detection of CRC has improved the overall survival (OS) rate up to 91%, improvement of the survival rate in the late-stage, such as stage IV CRC is the one that more efforts may be needed.

As summarized in a recent systematic review[4], the data from a total of 150 phase III clinical trials between 1986-2016 indicates that only 35 of 132 trials (26.5%) showed improved OS of patients more than two months. This summary clearly indicates that there are still many conditions to be addressed to significantly improve clinical outcomes. A nucleotide analog (fluorouracil) and a platinum drug (oxaliplatin) have been the mainstay in the first-line chemotherapy of CRC[5]. In addition, others such as a topoisomerase inhibitor (irinotecan)[6] and a pro-drug of fluorouracil (capecitabine) are also used[7,8]. However, microtubule (MT)-targeting drugs, such as taxanes, are not included in the current standard regimens for CRC.

In this review article, we would like to begin with a summary of the current standard treatment options and very recent examples [combination of vascular endothelial growth factor (VEGF) receptor signaling inhibition]. Then, we move on to discuss possible reasons why the MT cytoskeleton may not be a successful therapeutic target in CRC. Although cancer immune therapy is certainly one of the promising approaches to expanding the applications to CRC, cancer immunotherapy has also not been greatly successful in CRC to date. We would like to discuss a new class of MT inhibitors and their potential combination with light-“photopharmacology” toward the end.

CURRENT FIRST-LINE THERAPY OF CRC IN THE UNITED STATES

Because the high mortality of CRC is caused by late-stage CRC, a particular focus on the management of metastatic CRC (mCRC) would be critical to improving the OS of CRC patients. Based on the Centers for Disease Control and Prevention’s recent data, the current 5-year relative OS of mCRC is 15% (CDC <https://seer.cancer.gov/statfacts/html/colorect.html>). In addition to the traditional fluorouracil-based therapy (5-FU), a recent recommendation by the American Society of Clinical Oncology’s expert panel summarized more targeted therapy options based on molecular characteristics [9]. This guideline suggests doublet or triplet chemotherapy, depending on the subtypes of mCRC (Ras wild-type, BRAF V600E mutant) and certain microsatellite stable or proficient mismatch repair types. Briefly speaking, more personalized options are recommended in CRC management.

NEW COMBINATION THERAPIES IN 2023

There are a few newly reported combination chemotherapy regimens to treat refractory CRC in 2023. One of the reports was SUNLIGHT trial[10] utilizing the combination of bevacizumab (Avastin), trifluridine (FTD) and tipiracil (TPI; Lonsurf)[11]. The previously reported FTD-TPI combination, the third-line treatment option, already showed significant improvement in patient OS[12]. The addition of a humanized anti-VEGF-A antibody, bevacizumab[13], resulted in 144% increases in median OS (from 7.5 to 10.8 months) and a 230% increase in progression-free survival (2.4 to 5.6 months)[11]. These numbers are very significant improvements in advanced CRC management. FDA approved this combination

therapy in August, 2023[14]. We should note that bevacizumab can also inhibit angiogenesis; contraindication was reported among patients receiving bevacizumab, and lung and colon cancer patients have higher chances of contraindications based on the search of patients older than 65 years old[15].

The other notable targeted therapy reported in 2023 was FRESCO-2 trial using fruquintinib[16]. In this study, fruquintinib, a potent and orally administrable VEGF receptor tyrosine kinase inhibitor[17], was shown to improve median OS to 7.4 months compared to the placebo group (4.8 months). Although effective, we should note that grade 3 or worse adverse events were observed in 63% of the group receiving fruquintinib.

In summary, it is very clear that the combination of traditional DNA binding drugs and targeting of the VEGF signaling has shown superior OS in refractory/mCRC. However, we should carefully monitor the adverse effects associated with the inhibition of VEGF signaling.

LONG WAY TO DEVELOPING EFFECTIVE IMMUNOTHERAPY FOR CRC

Cancer immune therapy is one of the areas that is recently expanding its application to a variety of tumors. In CRC, an immune checkpoint inhibitor, pembrolizumab (Keytruda), is the only FDA-approved cancer immunotherapy drug for CRC so far (approved by FDA in 2017[18]). Theoretically, programmed cell death-1 (PD-1) blockage should be effective in helping CD8⁺ cytotoxic T cells target all tumor cells. Currently, high microsatellite instability/deficient mismatch repair (MSI-H/dMMR) locally advanced CRC patients may receive this treatment. In fact, a 2019 study showed increased programmed cell death-ligand 1 (PD-L1) expression in the tumor microenvironment of MSI-H/dMMR patients, suggesting that immune checkpoint inhibitors may be a great therapeutic target[19].

Since the rapid development of CRISPR-Cas9 technology, the use of chimeric antigen receptor-T (CAR-T) cells is the other strategy to target specific tumor-associated antigens[20]. Although a total of 25 CAR-T cell clinical trials for CRC are ongoing as of 2022[21], the application of CAR-T cell therapy to CRC faces a challenge because of the limited infiltration of CAR-T cells to the local tumor tissues, as discussed in detail[20]. This lack of infiltration is a major challenge in the application of CAR-T therapy to solid tumors in general. Unlike the successful approval of CAR-T therapy in hematopoietic malignancies[22], it will take a while until we find a way to successfully apply CAR-T therapy in CRC.

WHY TAXANES MAY NOT WORK WELL IN CRC

The MT-targeting drug, represented by taxanes, are well-established chemotherapeutic drug as represented by breast cancer treatment[23]. Besides breast cancer, paclitaxel and its derivatives are also a choice in ovarian, prostate, non-small cell lung, and gastric cancer[24]. However, MT-targeting drugs are not included in CRC chemotherapeutic regimens. One well-acknowledged fact is that CRC shows resistance to a wide spectrum of chemotherapeutic drugs, probably due to relatively high levels of P-glycoprotein. Compared to the spleen, stomach, ovary, skin, and lymphocytes, it was reported that the P-glycoprotein mRNA expression level in the colon is 6-30 times higher[25]. Thus, it makes sense that platinum-based DNA-targeting drugs are used as the first-line chemotherapeutic drugs in late-stage colon cancer management because platinum-based chemotherapeutic drugs covalently bind to DNA.

Table 1 summarizes the currently recruiting clinical trials including paclitaxel that target CRC. There are 13 trials (note that two of them study peritoneal carcinomatosis and anal cancer) and all others investigate combinational therapies. A small cohort of a phase II clinical trial conducted by MD Anderson Cancer Center's group tested the efficacy of albumin-conjugated paclitaxel (nab-paclitaxel)[26] on CRC as well as small bowel adenocarcinoma[27]. Although the trial demonstrated a promising result[25]. What we should note is that this clinical trial focused on a subset of CRC-CpG island methylator phenotype-and small bowel adenocarcinoma.

The doubling time of CRC cells is expected to be very long. The median doubling time of tumor volume was 130 d[28], thus, it would be fair to postulate that the doubling time of colorectal tumor cells may not be fast *in vivo*, unlike culture cell lines. This could be the other reason why MT-targeting drugs such as paclitaxel do not work well to treat CRC.

Docetaxel (Taxotere) is a semisynthetic analog of paclitaxel that was reported in 1991[29,30]. Because of its more potent activity, docetaxel has been quickly tried in many solid tumors. Nearly two decades ago, a phase II trial of docetaxel in mCRC was concluded[31]. Based on this trial, docetaxel showed little effect on mCRC treatment, unlike ovarian, breast, and non-small cell lung cancer. We do not know why the mouse CRC model system showed a very promising result[30]. Thus, basically, docetaxel is not recognized as an effective chemotherapeutic agent for CRC management[32]. Although docetaxel monotherapy may not be an option in CRC, it should be noted that there are a few potentially interesting experimental studies; RasSF10 suppresses CRC growth by activating p53 signaling to sensitize CRC cells to docetaxel[33], and this year, there is another study reporting the co-delivery of Akt inhibitor and docetaxel to CRC utilizing the CD44-targeted nanoparticles[34]. Thus, docetaxel may give more new combination therapy options than paclitaxel in the future. Table 2 summarizes the currently recruiting clinical trials including docetaxel in CRC. There is no phase III trial including docetaxel, and all recruiting trials add docetaxel as a part of the design.

Cabazitaxel is a more recently added, semi-synthetic paclitaxel analog that was approved by the FDA for the treatment of hormone-refractory metastatic prostate cancer[35]. Only one report has shown the suppression of CRC cell growth by activating p53 (using HCT116, LOVO, HCT8, and DLD1 cell lines as well as a xenograft model using HCT116)[36]. Thus, there is a potential to investigate the effectiveness of cabazitaxel in clinical settings, however, so far there are no cabazitaxel clinical trials for CRC.

Table 1 Recruiting colorectal cancer clinical trials that include paclitaxel

Clinical trial number	Treatment	Stage	Country
NCT05185947	Paclitaxel + nilotinib	Phase II	United States
NCT04731467	Nivolumab, Nab-paclitaxel, gemcitabine	Phase I/II	United States, Spain
NCT03129139	Minnelide™ + protein-bound paclitaxel	Phase I	United States
NCT05453825	Navicixizumab + paclitaxel or irinotecan	Phase II	United States
NCT05107674	NX-1607 (+ paclitaxel)	Phase Ia/b	United States, United Kingdom
NCT03678883	9-ING-41, gemcitabine, doxorubicin, carboplatin, Nab-paclitaxel, paclitaxel, irinotecan	Phase II	United States, Belgium, Canada, France, Netherlands, Portugal, Spain
NCT05395910	Paclitaxel	Phase I	Singapore (note: Peritoneal carcinomatosis)
NCT04666688	LYT-200, tislelizumab, gemcitabine + Nab-paclitaxel	Phase I/II	United States
NCT04444921	Carboplatin, nivolumab, paclitaxel	Phase III	United States (note: Anal cancer)
NCT04083599	GEN1042, pembrolizumab, cisplatin, carboplatin, 5-FU, gemcitabine, Nab-paclitaxel, pemetrexed, paclitaxel	Phase I/II	United States, Denmark, France, Georgia, Germany, Israel, Italy, Republic of Korea, Republic of Moldova, Spain, Taiwan, United Kingdom
NCT03872947	TRK-950, irinotecan, leucovorin, 5-FU, gemcitabine, cisplatin, carboplatin, ramucirumab, paclitaxel, nivolumab, pembrolizumab, imiquimod cream, bevacizumab, topotecan, PCD	Phase I	United States, France
NCT04644068	ADZ5305, paclitaxel, carboplatin, T-DXd, Dato-DXd, camizestrant	Phase I/II	United States, Australia, Canada, China, Czechia, Hungary, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, United Kingdom
NCT06047379	NEO212, ipilimumab, pembrolizumab, nivolumab, regorafenib, carboplatin, paclitaxel, FOLFIRI, bevacizumab	Phase I/II	United States

Table 2 Recruiting docetaxel study in colorectal cancer

Clinical trial number	Treatment	Stage	Country
NCT04553692	IGM-844 + FOLFIRI (+ bevacizumab) (docetaxel included as a part)	Phase I	United States
NCT04256707	Selinexor, docetaxel, pembrolizumab, FOLFIRI	Phase I/II	Israel
NCT02817633	TSR-022, nivolumab, TSR-042, 033, docetaxel, pemetrexed, cisplatin, carboplatin	Phase I	United States
NCT05714553	Fosifloxuridine nafalbenamide, leucovorin, pembrolizumab, docetaxel	Phase I/II	United Kingdom
NCT04895709	BMS-986340, 936558-01, docetaxel	Phase I/II	United States
NCT04894370	(Sample collection)	Phase II	France

In summary, taxanes have not been effective in treating CRC and thus have not been used as a choice in CRC management, although some clinical trials are going on, to combine either paclitaxel or docetaxel with other agents.

It is very interesting to note that sets of chemotherapy-induced gene expression signatures and the OS were correlated in breast cancer but not in CRC cells[37]. Cytokine responses to chemotherapeutic agents may be one of the potentially useful parameters to predict CRC to chemotherapy.

COMBRETASTATIN: A POTENT MT INHIBITOR

Based on the past research including clinical trials, MT is not a major target for the management of CRC. There is also a group of drugs that destabilize MTs, as represented by nocodazole. Nocodazole is mainly used to study MT functions and dynamics in cell biology—besides nocodazole, combretastatin might be a very interesting drug to study. Based on the information on medicinal and poisonous plants in Africa, the isolation of the first combretastatin was reported in 1982 [38], followed by several studies reporting structural analogs[39–41]. Originally isolated from an African tree, *Combretum*

caffrum, combretastatin is known as a very potent MT polymerization inhibitor[42]. Regardless of its discovery in the late 1980s, few applications of combretastatin have been studied until the 21st Century, maybe partly because of its very potent cytotoxicity. As seen in Table 3, there are only 19 clinical trials investigating combretastatin in all cancers (all are completed or terminated trials). It appears that the risk of adverse events is high. The high toxicity of combretastatin may probably be a part of the reasons that have hindered the application of combretastatin as a potential chemotherapeutic drug so far. Unfortunately, there is no combination trial of combretastatin in CRC; one clinical trial in Table 3[43] in anaplastic thyroid cancer shows that approximately 2-fold higher serious adverse events in the arm including CA-4 (+carboplatin and paclitaxel; 41.18%) compared to the control arm (carboplatin and paclitaxel only; 20.83%). The survival of combretastatin-including arm is 5.2 months (range: 3.1-9.0) and carboplatin and paclitaxel-only is 4.0 months (2.8-6.2), respectively. Thus, although the inclusion of combretastatin may slightly increase the survival period of patients, there is no statistically significant difference between both groups ($P = 0.223$). This, apparently no statistically significant difference, might be partly because of the relatively small scale of the study.

So, what would be the other option to develop CA-4-based therapy? Traditional development of natural compounds-based drugs will start by accomplishing the purification of the original, natural products[44]. From that point, total chemical synthesis of the original molecules will be tried, and then a variety of analogs will be synthesized to evaluate biological activities. More recently, biosynthetic bioengineering has also been considered as an alternative strategy[45]. CA-4 is not an exception. As reviewed by Hamze *et al*[46], there have been an astonishing 131 CA-4 analogs synthesized and tested from 2009 to 2019. Importantly, 114 out of 131 were tested with CRC cell lines (mostly HCT116). As detailed in this review, the natural CA-4 (*Z* (*cis*)-isomer) can be converted to the *E* (*trans*)-isomer by isomerization. The *E*-isomer is much less effective (GI_{50} is 80 times higher than *Z*-form). To prevent isomerization, the synthesis of a stable, non-natural isomer, *iso*CA-4 was reported by the authors' group in 2009[47,48]. The replacement of *cis*-/*trans*-bond between two trimethylphenyl rings with 1,1-diarylethylene structure made it possible to avoid isomerization meanwhile keeping the almost identical GI_{50} . Thus, newly developed panels of *iso*CA-4 analogs may be very promising as a monotherapy or combination therapy candidate.

More recently, CA-4 was shown to downregulate VEGF signaling *via* two different mechanisms: (1) Suppression of VEGF secretion in HUVEC as well as MCF-7 cell lines; and (2) VEGFR-2 expression and activation. Thus, CA-4 molecule itself already has two distinct activities: (1) MT destabilization; and (2) Anti-angiogenic activity[49]. This is essentially the same mechanism of action as the combination of paclitaxel (except paclitaxel polymerizes MT instead) and navicixizumab tried in ovarian cancer[50,51]. Therefore, the development of CA-4-based treatments may be still worth considering. In fact, a study using a mouse xenograft model showed that both the tumor growth curve, as well as the xenograft weight, were significantly reduced by the combination of CA-4[52].

OPTICALLY CONTROLLABLE COMBRETASTATIN

There have been some trials developing the area of "photo-pharmacology" utilizing photo-switchable drugs or light-induced activation of pro-drugs[53]. Because of its chemical structure, combretastatin molecules can exist in two different forms as described in the previous section; *i.e.*, *Z*- and *E*-forms. This means that the double-bond connecting two trimethylphenyl rings can result in interexchangeable *cis*- and *trans*-isomers. Because the *trans*-isomer is 80 times less effective in suppressing CRC cell growth, this isomerization has been reported to occur during storage and metabolism. Besides high toxicity, this is a potential pitfall-yet if we can control the conformation locally, CA-4 or its analogs may be very effective anti-cancer chemotherapeutic drug candidates.

Pro-drug would be one of the strategies to locally activate a drug. The first prodrug of CA-4 was reported in 2013[54]. In this study, the authors successfully convert the prodrug dithiaporphyrin-aminoacylate-CA-4 (CMP-L-CA-4) into CA-4 using 690 nm diode laser irradiation. The study used both breast cancer cell lines as well as an *in vivo* mouse model system. It is also notable that over 80% of this photo-cleavable CMP-L-CA-4 can release CA-4 in 10 min. IC_{50} was increased 6-fold after the irradiation[54]. The same group also developed different versions of prodrugs (Pc-(L-CA-4)₂ and Pc-(NCL-CA-4)₂). In those cases, approximately 26-28-fold increase in cytotoxicity was observed upon the release of CA-4 [55]. Although both are great photoactivatable CA-4, inactive prodrugs are only 6-28 times less toxic compared to CA-4. Thus, it is desired to keep inactive forms of CA-4 less toxic. Then, in 2015, photoswitchable photostatins (PST) were reported by the Trauner and Thorn-Seshould labs[56]. All PSTs replaced the C=C double bond connecting two trimethoxybenzene rings with the N=N double bond to give the azobenzene PSTs. In this study, the authors showed the comparison of eight different PSTs. One of them, the azologue of CA-4 phosphate, showed the best activation (101-fold activation upon photo-isomerization). Although all PSTs give μ M range of EC_{50} as *trans*-forms (inactive), the majority of *cis*-form (active) PSTs showed sub- μ M level EC_{50} . This is a very promising result, and supported by a few cell line-based experiments including poly(ADP-ribose) polymerase cleavage (a hallmark of apoptosis). Although spontaneous *cis* to *trans* isomerization occurs over minutes, a 75 ms pulse every 15 s can convert *trans* form to *cis* form quickly. More importantly, the authors confirmed the stability of PSTs-over 5000 times switches over two days. Thus, overall, PSTs are potentially promising, photoactivatable CA-4.

As discussed by Mulatihan *et al*[57], azobenzene reductase and NAD(P)H could cleave the N=N double bond in PSTs. Thus, it may be important to measure the elevation of azobenzene reductase level in experimental settings. Hypoxia is common in tumor microenvironment, and thus we may not underestimate azobenzene reductase's effect.

Table 3 The summary of clinical trials investigating CA-4 in cancer treatment

Clinical trial number	Conditions	Trial stage	Enrollment	Study period
NCT01570790	Age-related macular degeneration	Phase I/II	8	2003-2005
NCT01423149	Myopia	Phase II	23	2005-2007
NCT00060242	Head and neck cancer	Phase II	26	2003-2008
NCT00113438	Cancer (non-specified)	Phase II	23	2005-2007
NCT00960557	Neoplasm metastasis	Phase I	16	2009-2010
NCT00077103	Head and neck cancer	Phase I/II	4	2003-2007 (terminated)
NCT00003768	Adult solid tumor (unspecified)	Phase I	25	1998-2001
NCT00507429	Anaplastic thyroid cancer	Phase II/III	80	2007-2011 (terminated)
NCT01023295	Polypoidal choroidal vasculopathy	Phase II	20	2009-2010
NCT00395434	Tumors (unspecified)	Phase I	20	2006-2007
NCT02576301	Acute myelogenous leukemia/myelodysplastic syndromes	Phase I/II	105	2015-2020 (status unknown)
NCT00003698	Adult solid tumor (unspecified)	Phase I	35	1998-2003
NCT01085656	Acute myelogenous leukemia/myelodysplastic syndromes	Phase I	18	2011-2016 (terminated)
NCT02279602	Neuroendocrine tumors	Phase II	7	2014-2016
NCT00699517	Sarcoma	Phase III	355	2008-2013
NCT02132468	Neuroendocrine tumors	Phase II	18	2014-2016
NCT01701349	Anaplastic thyroid cancer	Phase III	0	2015-2017 (withdrawn)
NCT00653939	Non-small cell lung cancer	Phase II	63	2008-2011
NCT02641639	Platinum-resistant ovarian cancer	Phase II/III	91	2016-2017 (terminated)
NCT01240590	Anaplastic thyroid cancer	Phase I/II	27	2011-2016

DEVELOPMENT OF OTHER PHOTO-SWITCHABLE MT-TARGETING DRUGS

Because of its chemical structure (Figure 1), combretastatin is probably the easiest MT-targeting drug to control with light. Briefly speaking, there has to be one double bond ($R_1-C=C-R_2$ or $R_1-N=N-R_2$) to allow the conformational switching (*i.e.*, *cis vs trans*). It is very challenging to develop photo-switchable derivatives of other MT-targeting drugs, such as taxanes, because taxanes do not contain a C=C double bond suitable to induce photo-isomerization. Nevertheless, a few photo-switchable taxanes were developed very recently. The first report was published in 2020[58]—it used paclitaxel as the base and added azobenzene to one of the side chains because taxanes have no double bonds in their core structures that allow photo-isomerization. In this first report, careful selection of the modified side chain (Figure 2, top arrow) was made based on the distance of side chains from paclitaxel's target, β -tubulin. Because a fluorescent dye-conjugated taxane was made by coupling a fluorophore at the 3'-amino group[59], and such fluorescently label taxanes still retained the ability to bind to MTs. Among 10 derivatives that the authors synthesized, the substitution of the benzamide side chain of paclitaxel with OCH_3 -azobenzene (in *meta* configuration) gave the most effective compound, AzTax3MP (Figure 2, top). AzTax3MP changes the EC_{50} from 1.4 to 0.24 μM upon shining with 360 nm LED light[58]. This research is certainly a great pharmacological advance, as paclitaxel has been used in several types of solid tumor management for a long period of time[24]. One potential disadvantage is the dynamic range of the toxicity before and after photo-switching. Photo-switching only increases the IC_{50} by less than 6-fold. The following study[60] initially attempted the development of a photo-switchable docetaxel analog (SBTax) by conjugating SBTub to docetaxel. To create SBTax, the addition of the styrylbenzothiazole needed to be conjugated to the amino group of the side chain of docetaxel (Figure 2, bottom arrow). However, the low solubility and bioactivity of SBTax precluded it from an ideal photo-switchable MT drug in this case.

In the same study[60], the authors then explored the synthesis of photo-switchable epothilone analogs. The authors also pointed out the potential advantages of epothilones because of their high solubility in water and the ability to cross the blood-brain barrier. Although epothilones have one C=C double bond at the side chain, this double bond may not be suitable for photo-isomerization because it is adjacent to the core ring structure. Therefore, the installation of an extending photo-switchable group was tried. Among several modifications, the author mentioned that the compound STEpo2 (styrylthiazole group coupled to the core structure of epothilone D; Figure 3) showed better synthetic access and the highest cytotoxicity upon photo-switch ($IC_{50} = 0.1 \mu M$). It appears that STEpo2 and a few derivatives can show up to 4-fold potency change.

In summary, very recently, photo-switchable compounds were derived from clinically-proven MT-targeting drugs. However, right now, the dynamic range of potency shift is not comparable to what is seen in combretastatin analogs (combretastatin and its photo-switchable derivatives showed a 60-100+-fold potency shift). In addition, taxanes were not

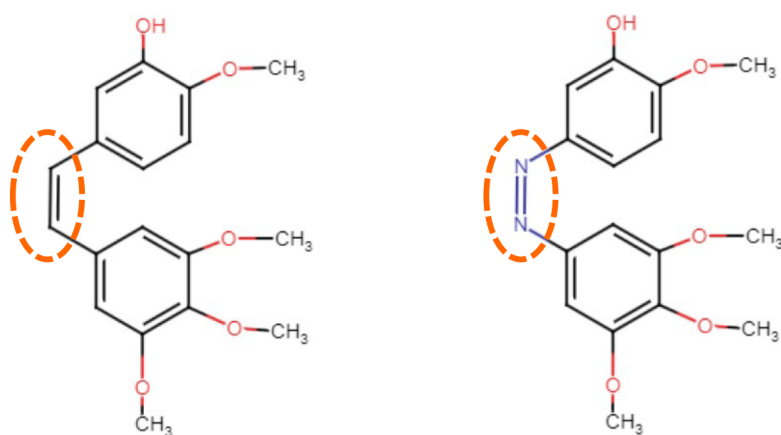


Figure 1 The chemical structures of combretastatin CA-4 (left) and photostatin photoswitchable photostatins-1[56]. Both compounds have either the C=C or N=N double-bond that can induce photo-isomerization by light (circle).

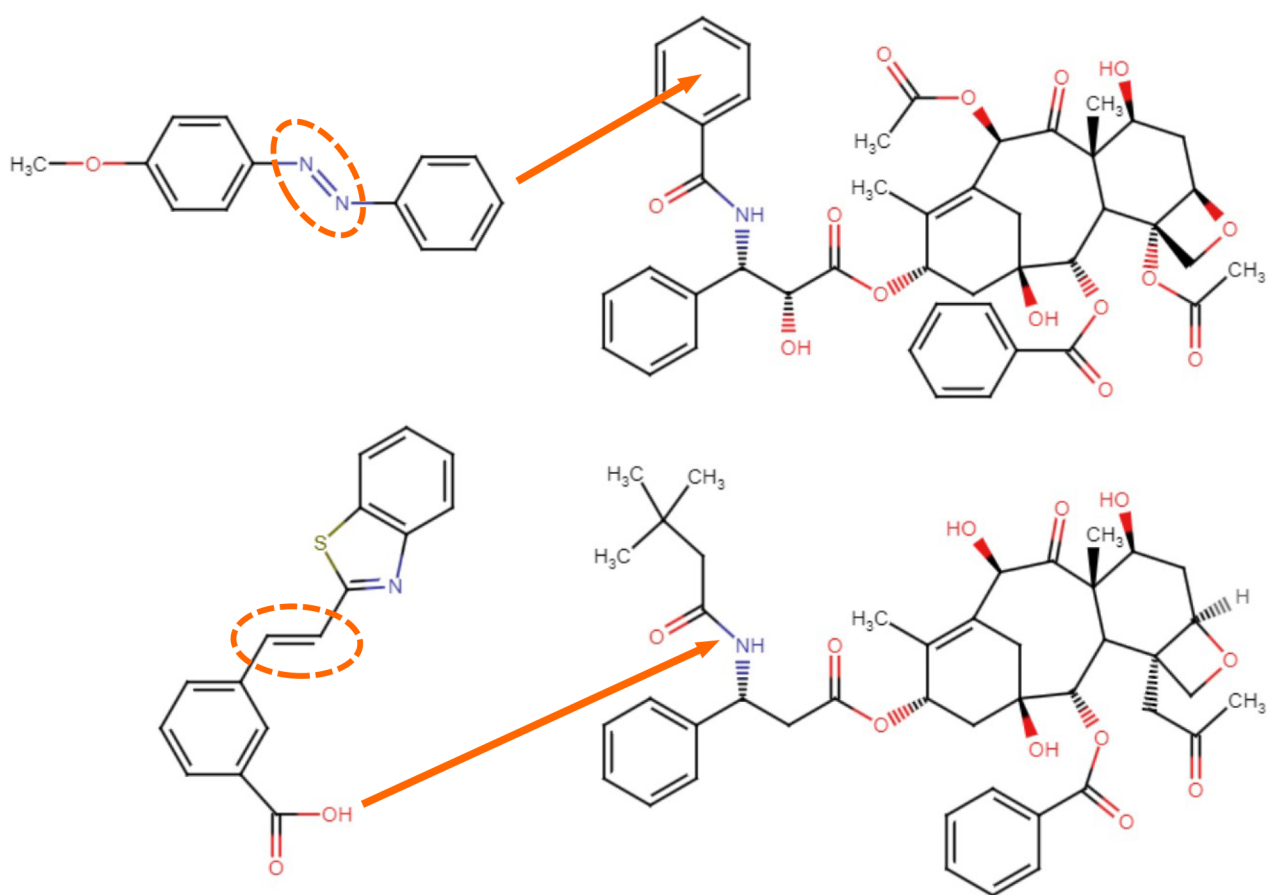


Figure 2 The chemical structures of paclitaxel (top right) with an azobenzene derivative (top left) and docetaxel with a styrylbenzothiazole derivative (bottom). The photo-switchable C=C or N=N double-bond is highlighted (dotted circle). Each group is conjugated to the left arm of taxanes (arrows), resulting AzTax3MP[58] and SBTax[60], respectively.

successful in CRC management in past clinical trials. Therefore, we think that combretastatin analogs might hold better promise to develop clinically applicable, photo-controllable drug candidates.

DEVELOPMENT OF ENDOSCOPY CAPABLE OF HANDLING TWO-PHOTON ILLUMINATION

To convert photo-switchable combretastatin to the active form, a relatively short wavelength (390 nm) is required. Although it is not a UV range, a longer wavelength is preferred to avoid DNA damage. Two-photon excitation would be a great solution to avoid damages generated by short wavelengths, and more importantly, longer, near-infrared red light

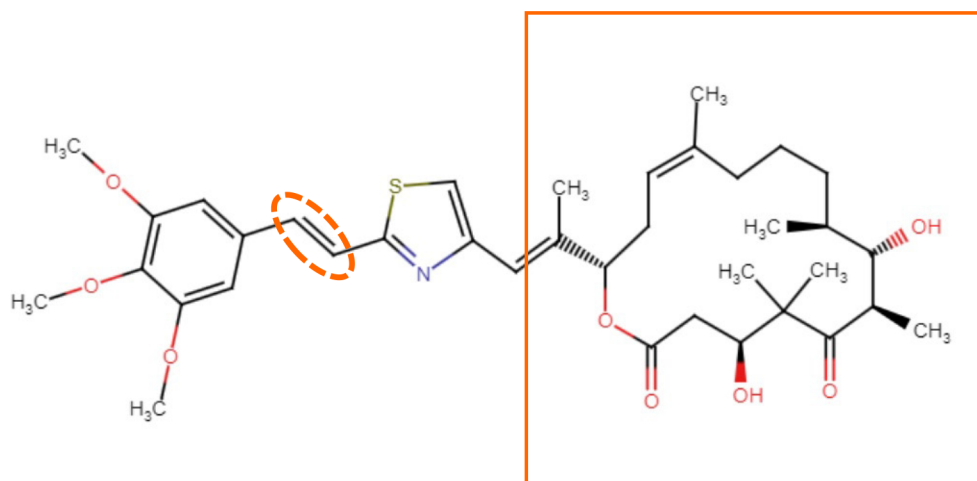


Figure 3 The chemical structures of STEpo2[60], a photo-switchable derivative of epothilone D. The photo-switchable C=C double-bond (dotted circle) in the attached styrylthiazole group. The rectangle indicates the core structure of epothilone D.

can penetrate deep inside tissue. The first two-photon fluorescence microscopy was reported by Denk *et al*[61]. However, two-photon excitation utilizes a giant femto-second pulse laser, and thus initially it was very difficult to apply two-photon excitation to *in vivo* applications. The development of optical fiber technologies enables us to guide the two-photon excitation beam into tissues[62-65]. This development allowed the application of two-photon excitation for colon cells[66], and the first clinical two-photon endoscope was reported in the same year[67]. There is no report trying the photo-activation of CA-4 analogs *in vivo* so far. We look forward to seeing CA-4-based photopharmacology.

To our knowledge, the first report of a photopharmacological approach reporting the photo-activation of a prodrug appeared in 2013[68]. The study showed local activation of doxorubicin prodrug using a mouse model system and fiber optics. The mixture of A549 human non-small cell lung cancer cells and matrigel were injected into flanks of nude mice, thus, the condition may be a little artificial. This doxorubicin prodrug is cleaved and releases the active, doxorubicin. One very important message from this preliminary study is that: (1) Doxorubicin was not detected in serum before the local photoactivation; and (2) After photoactivation, doxorubicin stayed a little (30 min after light exposure) in the local tissue and was not immediately detected in the collected serum. Thus, the concept of “photopharmacology” was shown *in vivo* for the first time in 2013.

Although it is not related to combretastatins, endoscope-assisted phototherapy was carried out using a photoswitchable proteasome inhibitor and HCT-116 human CRC cell line recently[69]. Thus, photopharmacology was achieved with a CRC cell line model system.

CONCLUSION

Because of the increasing incidence of CRC in younger age groups, it is increasingly important to further develop better treatment options for CRC, especially mCRC. Current first-line therapy regimens have been built around platinum and nucleotide analogs, yet the combination of other signaling, such as VEGF signaling inhibitors, showed promising results in recent clinical trials. Because of its role in fundamental biological processes, MT should be an important target in clinical oncology, as we have seen in other solid tumor management. However, MT inhibitors alone have not been successful in CRC management. Currently, there are clinical trials investigating the combinations of taxanes and other agents in CRC. Meanwhile, we should look forward to the other promising MT inhibitors. Here, we reviewed some promising recent clinical trials, mainly promising combination therapies. Our main interest is how we can develop MT-targeting drugs more effective for cancer types that did not show good clinical responses in the past. Then we introduced one potential solution that may allow effective, local activation of drugs using light-photopharmacology. Light-induced isomerization has great potential to achieve local activation of very potent drugs, which are usually too harmful, such as combretastatin. The unique chemical structure of combretastatin CA-4 and the developed prodrugs and PSTs also showed a very effective potency shift[56] that is promising to further develop them for pre-clinical applications. Although more recent studies attempted to synthesize photo-switchable taxanes and epothilone derivatives[58,60], their narrower potency shift may make them less ideal right now for pre-clinical applications. With the recent advance of fiber optics and a proof-of-concept study, it may be time to design a new MT drug with the power of light.

FOOTNOTES

Author contributions: Kita K and Burdowski A conceived the idea and wrote the manuscript.

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