International Journal of Clinical Oncology and Cancer Research
2024, Vol. 9, No. 3, pp. 44-51
https://doi.org/10.11648/j.ijcocr.20240903.12

Commentary

CDA Formulations: Potentially the Standard Care of Breast, Lung and Liver Cancers

Ming Cheng Liau*, Christine Liau Craig, Linda Liau Baker

CDA Therapeutics, Inc. 3308 Sky Run Court, Missouri City, United States

Abstract

Breast and lung cancers are very common, which are the top two leading causes of death from cancer. Hepatomas are not as common. But hepatomas are not responding well to therapies currently available. Cancer incidence and mortality keep on increasing ever since these statistics became public records, which are an indication of the failure of the health profession to control cancer. Cancer therapies approved in the past are mostly based on killing of cancer cells which are wrong to solve only a fraction of cancer problems. To effectively solve cancer, we must eliminate all factors contributing to the evolution of cancer. Cancer evolves due to wound unhealing because of the collapse of chemo-surveillance. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs), which are embryonic stem cells to initiate the development of organs and tissues. Methylation enzymes (MEs) play a pivotal role on the regulation of cell replication and differentiation. Because of this pivotal role, MEs are exceptionally subjected to double allosteric regulations, on the individual enzymes by steroid hormone and on the enzyme complex by telomerase and chemo-surveillance. MEs of embryonic stem cells (ESCs) including PSCs are abnormal due to association with telomerase, which are important for the functions of these cells for the development of fetus and wound healing. The build-up of normal stem cells with abnormal MEs is strictly under regulations by contact inhibition, ten-eleven translocator -1 (TET-1) enzyme to direct lineage transitions and chemo-surveillance to destabilize abnormal MEs. When such safety mechanisms fail, clinical symptoms arise. Obviously, the most appropriate solution of diseases due to wound unhealing is to restore safety mechanisms created by the nature. Cell differentiation agent -2 (CDA-2) is our creation of cancer drug to target on abnormal MEs. CDA-2 was approved by the Chinese FDA as an adjuvant to supplement cytotoxic therapy of cancer against breast, non-small cell lung cancers and primary hepatomas in 2004, and as a mono-therapeutic agent for the therapy of myelodysplastic syndromes (MDSs) in 2017. MDSs are diseases attributable entirely to cancer stem cells (CSCs). CDA-2 was the best drug for the therapy of MDSs, and therefore should be considered the standard care of MDSs. Breast, non-small cell lung cancers and primary hepatomas responded well to CDA-2. The therapeutic end point of CDA-2 is the terminal differentiation of cancer cells which cannot make tumor to disappear. Evidently, terminal differentiation of CSCs is the only option to solve CSCs. The solution of CSCs is very critical to the success of cancer therapy. Therefore, CDA formulations are potentially the standard care of breast and lung cancers and primary hepatomas.

Keywords

Breast, Lung and Liver Cancers, CDA, Chemo-Surveillance, CSCs, DIs, DHIs, PSCs, Wound Healing

*Corresponding author: mingliau@yahoo.com (Ming Cheng Liau)

Received: 16 October 2024; **Accepted:** 30 October 2024; **Published:** 28 November 2024

1. Introduction

Breast and lung cancers are very common, which are the top two leading causes of death from cancer among women. Lung cancer is also the top leading cause of death from cancer among men. Hepatomas are not as common as breast and lung cancers. But hepatomas are not responding well to cancer therapies currently available. Cancer incidence and mortality keep on increasing ever since these statistics became public records. The latest statistics of 2019 showed cancer incidence of 19 million and cancer mortality of 10 million worldwide, which were 5.0% and 5.3% increment of the 2018 statistics according to NCI [1]. The NCI experts predicted annual increment of 5% likewise in the following years. Cancer statistics of the USA are better. The latest statistics of 2023 showed cancer incidence of l.96 million and cancer mortality of 0.61 million, which were 2.0% and 0.2% increment of the 2022 statistics according to American Cancer Society [1]. The ever-increasing cancer mortalities are an indication of the failure of health profession to control cancer. Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells. Cytotoxic chemotherapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard gas bombs were employed. Victims of toxic gas all displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Cytotoxic chemicals thus became standard drugs for the therapy of cancer patients, and the disappearance of cancer cells in the case of hematological cancers and the disappearance of tumor in the case of solid cancers became the standard criteria for the evaluation of efficacy of cancer therapy. Both were wrong. But the mistakes carried on. When President Nixon declared War on Cancer in 1971, cytotoxic chemotherapy and radiotherapy were the major cancer drugs employed, which failed to reduce cancer mortality. A presidential project can only last 5 years with unlimited support from national resources. It was fair to make a conclusion if the therapeutic approach has been drilled through as a presidential project and failed, that therapeutic approach must not be adequate for cancer therapy. Apparently, cancer establishments agreed to the conclusion to search for other therapies. They shifted to gene therapy during 1976-1996, which was not successful because it was too difficult and too expensive to develop gene therapy, and then to anti-angiogenesis therapy during 1996-2016, which was also not successful, because the therapy resulted in patients' deaths due to internal bleeding, and then to immunotherapy from 2016 on ward [2]. Meanwhile, cancer establishments kept on using failed cytotoxic agents to treat cancer patients, resulting in continuous increase of cancer mortality. To effectively solve cancer, we must thoroughly examine how cancer evolve, and try to eliminate all elements important in the contribution of cancer evolution.

2. Commentaries and Discussion

2.1. Cancer Evolves Due to Wounds Unhealing

The concept of cancer evolves due to wound unhealing was introduced by the great German scientist Virchow in the 19th century [3]. It was again brought up by Dvorak in 1986 [4]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [5]. We provided the most important details on this subject that included abnormal MEs to block differentiation [6-8]; chemo-surveillance as the nature's creation of allosteric regulation on abnormal methylation enzymes to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing [9-11]; DIs and DHIs as wound healing metabolites and also as the active players of chemo-surveillance [9-11]; hypomethylation of nucleic acids as a critical mechanism of terminal differentiation [12]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [13-15]; and the evolution of CSCs from PSCs due to wound unhealing [16]. These studies very convincingly establish that cancer evolves due to wound unhealing. The failure to heal wound is obviously attributable to the collapse of chemo-surveillance.

The seed of cancer is sawed at the very beginning of life, namely the fertilization of egg to activate totipotent stem cell which expresses abnormal MEs. Abnormal MEs are spread through embryonic stage to develop the fetus to become a perfect baby. Interruption of the function of abnormal MEs is detrimental for the development of the fetus. Thalidomide which interrupts the function of abnormal MEs causes malformation of limbs. The blockade of differentiation by abnormal MEs is necessary to build up cells needed for the development of the fetus or for the heal of the wound. The build up of cells with abnormal MEs is strictly regulated by contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance, which are safety mechanisms to prevent the build up of cells with abnormal MEs to become clinical problems. Abnormal MEs are not a problem of embryonic stem cells because embryonic stem cells are well under control. They become a critical issue of cancer because of the collapse of safety mechanisms [17]. Chemo-surveillance is the final defense to prevent cells with abnormal MEs to get out of control. The maintenance of chemo-surveillance becomes the top priority for the therapy of cancer [18]. The employment of phenylacetylglutamine to protect and to restore the functionality of chemo-surveillance has proved very effective for the chemoprevention of cancer [19] and for the therapy of early stage cancer patients [9]. It is clear that the collapse of chemo-surveillance is responsible for wound unable to heal. But the nature does not a mechanism to detect the collapse of chemo-surveillance to rectify. Instead, PSCs are forced to proliferate. The proliferation of PSCs is restricted by contact inhibition. So, they are forced to evolve into CSCs to escape the restriction of contact inhibition. It

takes a single hit to silence TET-1 enzyme to turn PSCs into CSCs, which is an easy task for PSCs to accomplish since these cells are equipped with abnormally active MEs. The proliferation of CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance. The pressure of chromosomal abnormalities set in to increase the proliferation of CSCs to become faster growing cancer cells (CCs) by the activation of oncogenes or the inactivation of suppressor genes to become a full-blown cancer problem. Therefore, chemo-surveillance, CSCs and CCs are all critically involved in the evolution of cancer. An effective cancer drug must be able to eliminate CSCs, CCs and to restore the functionality of chemo-surveillance [20]. The emergence of CSCs is critically linked to wound unhealing. The solution of CSCs is also critically linked to wound healing. Therefore, induction of terminal differentiation of cells with abnormal MEs, which is a critical mechanism of wound healing [13], is the only option to solve the issue of CSCs [21]. CSCs became a known issue around 2006 [22]. Subsequently, CSCs were identified as the cells responsible for metastasis, drug resistance, angiogenesis, unresponsiveness and recurrence [23-27], which are the major fatal effects of cancer. Apparently, the solution of CSCs is very critical to the success of cancer therapy. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [28]. Of course, cancer establishments knew the importance of CSCs. The pharmaceutical giant GSK put up 1.4 billion around 17 years ago to acquire monoclonal antibodies against CSCs developed by the scientists of Stanford University, the highest amount to develop a cancer drug. Monoclonal antibodies failed to solve CSCs. Killing of CSCs by antibodies or by other means is not an option to solve CSCs. CDA formulations are the only viable option to solve CSCs. The solution of CSCs is critical to the success of cancer therapy. Therefore, CDA formulations are the only drugs best to solve cancer [29]. CDA formulations are the prescriptions of the nature to ensure perfection of wound healing, which are also the prescriptions of the nature for cancer therapy [30-33]. Cancer establishments blocked cancer drugs that could not cause the tumor to disappear, that essentially killed the possibility for the approval of CDA formulations, the best drugs to solve CSCs to reduce cancer mortality [29]. Cancer incidence keeps on increasing, which is unavoidable as industrialization that causes pollution to promote cancer development is needed for the advancement of the nation. The ever-increase of cancer incidence and the blockade of effective cancer therapy with CDA formulations by cancer establishments is the reason cancer mortality keeps on increasing.

2.2. CDA-2 as the Best Drug for the Therapy of MDSs

Cancer evolves due to wound unhealing as above described. Naturally the most appropriate therapy of cancer is to follow wound healing process [31-33]. CDA-2 is a preparation of wound healing metabolites purified from freshly collected urine by reverse phase chromatography on XAD-16 [34]. The active ingredients include arachidonic acid or dicycloprostaglandins as DIs in association with pregnenolone as liposomal complexes, designated as OA-(0.43-0.52) or with membrane fragments, designated as PP-0 [35-37], uroerythrin, pregnenolone and possibly other steroid metabolites as DHIs [38-40], and phenylacetylglutamine as anti-cachexia chemical [9, 19]. DIs or DHIs can be very good cancer drugs. All-trans retinoic acid, an excellent DI, is the standard care of acute promyelocytic leukemia [41] and Gleevec, an effective DHI, is the standard care of chronic myeloid leukemia [42]. Differentiation inducing agents are definitely excellent cancer drugs, but they are not favored by cancer establishments because they cannot make tumor to disappear. The situation has changed. These are the only drugs able to handle CSCs [21].

MDSs are a classic case to demonstrate the evolution of cancer due to wound unhealing. MDSs often start with a display of an immunological disorder triggered by wound [43], which prompts the local production of inflammatory cytokines. Among cytokines produced, TNF is the critical factor related to the development of MDSs as antibody of TNF has been shown effective to halt the progress of MDSs [44]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells, such as erythrocytes, platelets or neutrophils. TNF is also named cachectin after its notorious effect to cause cachexia symptoms, which are commonly shared by inflammatory and cancer patients. A characteristic disorder of cachexia symptoms is the excessive urinary excretion of low molecular metabolites leading to the collapse of chemo-surveillance, which is the nature's creation of allosteric regulation on abnormal MEs to avoid the build up of cells with abnormal MEs [45]. The high level of telomerase in the peripheral and bone marrow leukocytes in MDSs patients is an indication of the widespread multiplication of malignant cells [46, 47]. The propagating pathological cells have been identified as human CSCs [48]. So, MDSs represent cancer development at the stage of CSCs, which are ideal for the test of drugs effective against CSCs.

Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDSs by the Chinese FDA. Vidaza and Decitabine are also approved for the therapy of MDSs by the US FDA.

Professor Jun Ma, the Director of the Harbin Institute of Hematology and Oncology, was instrumental in conducting the clinical trials of all three MDSs drugs approved by the Chinese FDA. According to his assessments based on two cycles of treatment protocols, each 14 days, he found CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and markedly better therapeutic efficacy based on hematological improvement evaluation, namely on the dependency of blood transfusion as shown in Figure 1, which is reproduced from the reference [49].

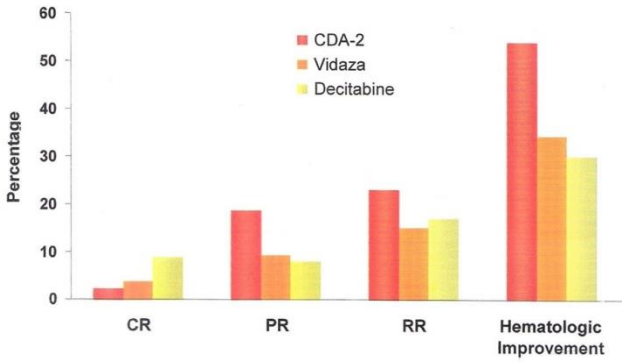

Figure 1. *Relative Effectiveness of MDSs Drugs.*

Inactivation of abnormal MEs is the critical mechanism to achieve therapy of MDSs. It is the same mechanism to achieve wound healing [13]. CDA-2 achieves inactivation of abnormal MEs by the elimination of telomerase from abnormal MEs which is a selective tumor factor [8, 21, 29, 30, 33, 34], whereas Vidaza and Decitabine achieve inactivation of abnormal MEs by covalent bond formation between DNA methyltransferase and 5-aza-cytosine base incorporated into DNA [50]. The action of CDA-2 is selective toward cancer cells, thus without adverse effects, whereas the action of Vidaza and Decitabine is non-selective, which can also affect normal stem cells to result in severe DNA damages [51-53]. Vidaza and Decitabine are proven carcinogens [54, 55]. The contrast is very clear that CDA-2 is the drug of choice for the therapy of MDSs. The success of cytotoxic therapies of cancer relies on the restoration of chemo-surveillance to subdue surviving CSCs which are resistant to cytotoxic therapies because CSCs are protected by drug resistant and anti-apoptosis mechanisms. Only the early stage cancer patients whose chemo-surveillance have not yet fatally damaged can benefit from cytotoxic therapies [2, 14, 18, 29, 31-33]. Cytotoxic agents are responsible for the death of the majority of cancer patients in the advanced state whose chemo-surveillance have been fatally damaged beyond recovery by pushing these patients to become unresponsive, or even still responsive to reach complete remission and then to succumb to recurrence [2, 14, 18, 29, 31-33]. In final analysis, CDA formulations are the only cancer drugs that can save advanced cancer patients [29]. Unfortunately, cancer establishments set up a rule of tumor shrinkage to deny the acceptance of CDA formulations as cancer drugs. That rule is the culprit for cancer mortality to keep on increasing.

2.3. CDA Formulations: Potentially the Standard Care of Breast, Lung and Liver Cancers

Clinical trials of CDA-2 for cancer therapy took place between 1994-2004 in China. Breast cancer responded most favorably to CDA-2, followed by non-small cell lung cancer and primary hepatomas [56]. Lung cancer is the top killer of male and female cancers and breast cancer is the second leading killer of female cancers [1]. It was encouraging that CDA-2 showed effectiveness against top killers. Breast cancer is the most responsive cancer to therapies, because it is externally located easier for early detection. In addition, there are multiple therapeutic opportunities such as tamoxifen and aromatase inhibitor against estrogen and progesterone, trastuzumab against Her-2 which are only good for breast cancer. Yet breast cancer is the second leading cause of death from cancer among women. Triple negative clone, which is most likely CSCs, produces the major fatal effect. CDA-2 is good for the therapy of CSCs, which must be an important factor to dictate the responsiveness of breast cancer to CDA-2. Likewise, the favorable response of lung and liver cancers to CDA-2 can also be attributed to the therapy of CSCs.

CDA-2 was approved by the Chinese FDA for the therapy of breast cancer, non-small cell lung cancer and primary hepatoma as an adjuvant agent to supplement chemotherapy [56]. It was effective as a mono-therapeutic agent, but the reduction of tumor shrinkage was not remarkable to fulfill the request as a mono-therapeutic cancer drug. The issue of CSCs became known around 2006 [22]. We were unaware at that time that CDA-2 was the only option for the eradication of CSCs. We are now in a position to claim that CDA-2 is the drug of choice for the therapy of breast and lung cancers, as the evidence showed that CDA-2 is the best drug for the therapy of MDSs. CDA formulations are the only drugs that can effectively reduce cancer mortality [29]. So, CDA formulations are potentially the standard care of breast, lung and liver cancers. Only the acceptance of CDA formulations can we expect to see the drop of cancer mortality [29]. So, the acceptance of CDA formulations as the standard care of breast, lung and liver cancers is a right move to reduce cancer mortality.

2.4. Development of CDA Formulations as the Standard Care of Breast and Lung Cancers

We have carried out extensive studies of the natural DIs and DHIs present in the urine and unnatural DIs and DHIs for the manufacture of CDA formulations as the standard care of breast, lung and liver cancers [34-40], which are summarized in Tables 1 and 2. ATRA is an exceptionally active DI, which is the standard care of acute myeloid leukemia [41]. It requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to achieve the therapeutic effect [57]. The product of this enzyme, oligoisoadenylate, is the actual DI to act on abnormal MEs. PGJ2 is the most active DI of PG derivatives. PGs are unstable metabolites with very short half lives measured by minutes [58], which are not suitable as DIs of CDA formulations. PGE2 is a biological response produced at the initial stage of wound [59]. The potent inflammatory activity of PGs [60] rather than DI activity to orchestrate the initial response of wound is the purpose of PGs production, resulting in edema for the ex-

travasation of growth inhibitory factors such as DIs and DHIs for PSCs to proliferate [13]. The promotion of PGs as DIs is probably not a good idea. The employment of stable end products of PGs or their substrate AA, although less active, is a better choice. BIBR1532 is a telomerase inhibitor, which is the only choice of unnatural DI for the manufacture of CDA formulations.

Table 1. Active Dis.

DIs	ED_{25} (μM)	ED_{50} (μM)	ED_{75} (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	40.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

For the induction of terminal differentiation, DIs are more important than DHIs. But the inclusion of DHIs is also crucial to achieve better therapeutic result. The use of DIs alone cannot result in the induction of all cancer cells to undergo terminal differentiation, because in the presence of DIs alone, MEs tend to be dissociated to become individual enzymes. MTs in the monomeric state are vulnerable to be modified to become nucleases that can cause damages to replicating DNA. The damaged cells become senescent cells. After repair, senescent cells can bounce back to cause recurrence. In the presence of DHIs, particularly the inhibitors of SAHH and MT, the modification of MTs to become nucleases can be prevented by keeping MT-SAHH as dimeric complex or by interfering the modification process. So, in the presence of DHIs, terminal differentiation can reach completion to avoid recurrence.

Table 2. Active DHIs.

SAHH Inhibitors	$RI_{0.5}$ (μM)	STIs	$RI_{0.5}$ (μM)
Pyrivinium Pamoate	0.012	Sutent	0.28
Vitamin D_3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	Polyphenols	$RI_{0.5}$ (μM)
Pregnenolone	7.16		
		Tannic Acid	0.37
MT Inhibitors	$RI_{0.5}$ (μM)	EGCG	0.62
		Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
		Genisteine	2.19
MAT Inhibitors	$RI_{0.5}$ (μM)	Pyrogallol	3.18
		Silibinine	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagoc Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phlorogluc i l-lnol	38.82

Inhibitors of SAHH and MT are better DHIs. This is because MAT is the most stable enzyme of the three MEs. The association with telomerase further increases its stability. It is very difficult to shake loose of this enzyme in the abnormal MEs configuration. Pregnenolone is a major DHI of CDA-2 [35]. It is a single metabolite to profoundly influence the evolution of cancer. According to Morley [61], the production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at 20-25 years old. The youngest and the oldest people produce relatively the smallest amounts. These are the two age groups most vulnerable to develop cancer. It is our choice of DHI for the manufacture of CDA-CSC to target CSCs. The finding of signal transduction inhibitors (STIs) as excellent DHIs is expected, since signal transductions tend to produce factors to stabilize MEs. STIs are naturally excellent DHIs. The finding of polyphenols as excellent DHIs is a surprise, but is a pleasant surprise. Polyphenols are generally considered good for health. The finding of polyphenols as excellent DHIs enhances their credibility as heathy foods.

Effective CDA formulations can be ED_{25} of a DI + 3x$RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2x $RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [35]. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI. $RI_{0.5}$ of a DHI can be determined by the procedure previously published [38]. We have previously noticed that not all cancer patients responded favorably to the therapy of Antineoplastons, which were preparations of wound healing metabolites purified from urine by reverse phase chromatog-

raphy on C18 [62]. CDA-2 and Antineoplastons are similar preparations of wound healing metabolites purified by reverse phase chromatography. CDA-2 is purified by XAD-16 and Antineoplastons are purified by C18. PP-0 is a major active component of CDA-2, which is only a minor active component of Antineoplastons, whereas peptides are major active components of Antineoplastons which are not present in CDA-2. The antitumor mechanisms of CDA-2 and Antineoplatons are basically the same by targeting on abnormal MEs to induce terminal differentiation of cancer cells. The active components of Antineoplastons are low molecular weight metabolites, which may be easily degraded. Cancer cells are known to express a high level of degradative enzymes to salvage substrates for the syntheses of macromolecules to promote faster growth. Low molecular weight natural active DIs and DHIs may be easily degraded to lose activity. Thus, we recommend to put up two sets of CDA formulations: one set to target CSCs consisting of natural DIs and DHIs for easy access to CSCs, and another set to target CCs consisting of unnaturasl DIs and DHIs to resist degradative enzymes of faster growing CCs. CDA-CSC can be plasma concentrations of ED_{50} of AA + $2xRI_{0.5}$ of pregnenolone, and CDA-CC can be plasma concentrations of ED_{50} of BIBR1532 + $2xRI_{0.5}$ of pyriminium pamoate. In addition, the inclusion of phenylacetylglutamine is very helpful to prevent the loss of therapeutic agents and to restore chemo-surveillance.

The approval of CDA formulations as potential standard care of breast, lung and live cancers is a good beginning to save cancer patients. A lot of work remains to be done such as establishing easy tests of therapeutic end point and chemo-surveillance. These are technical problems that can be overcome.

3. Conclusion

Cancer evolves due to wound unhealing. Healing wound is the most appropriate approach of cancer therapy. CDA-2 is a preparation of wound healing metabolites purified from freshly collected urine, which was approved by the Chinese FDA for the therapy of MDSs as a mono-therapeutic agent, and for the therapy of breast, lung and liver cancers as an adjuvant agent to supplement cytotoxic cancer therapies. It turns out that CDA-2 is the best drug for the therapy of MDSs which are diseases attributable entirely to CSCs. CDA-2 has shown excellent therapeutic effects on breast, lung and liver cancers. The effectiveness of CDA-2 against CSCs is the reason for its superior therapeutic efficacy on these cancers. CDA formulations are potentially the standard care of breast, lung and liver cancers. Lung cancer is the leading cause of death among male and female cancers and breast cancer is the second leading cause of death among female cancers. CDA formulations may play a significant role to reduce cancer mortality.

Abbreviations

AA	Arachidonic Acid
AdoHcy	S-adenosylhomocysteine
AdoMet	S-adenosylmethionine
ATRA	All-trans Retinoic Acid
CCs	Cancer Cells
CDA	Cell Differentiation Agent
CSCs	Cancer Stem Cells
DI	Differentiation Inducer
DHI	Differentiation Helper Inducer
ED	Effective Dosage
EGCG	Epigallocatechin Gallate
ESC	Embryonic Stem Cells
MEs	Methylation Enzymes
MT	Methyltransferase
RI	Reductive Index
SAHH	S-Adenosylhomocysteine Hydrolase
STIs	Signal Transduction Inhibitors
TET-1	Ten-Eleven Translocator-1

Acknowledgments

We are grateful for the support of the development of CDA formulations by Professor John P. Fruehauf of Chao's Family Comprehensive Cancer Center of University of California Irvine Medical Center. We appreciate very much the encouragement of President Joe Biden on the development of CDA formulations through personal communications, who has expressed a desire of collaboration to fulfill the cancer moonshot initiative he brought up in 2022.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Google search on cancer statistics-NCI, ACS.

[2] Liau MC, Craig CL. Wound healing metabolites to heal cancer and unhealed wounds. Intl Res J Oncol. 2020; 6(3): 8-20.

[3] Virchow R. Die Cellular Pathologie in Ihrer Begrundung auf Physiologische und Pathologische Gewebelehve. Hirschwald. 1858; 16: 440.

[4] Dvorak HF. Tumors: Wounds that do not heal. N Engl J Med. 1986; 315(26): 1650-1659.

[5] MacCarthy-Morrough L, Martin P. The hallmarks of cancer are also the hallmarks of wound healing. Science Signaling. 2020; 13: 648.

[6] Liau MC, Lin GW, Hurlbert RB. Partial purification and characterization of tumor and liver S-adenosylmethionine synthetases. Cancer Res. 1977; 37(2): 427-435.

[7] Liau MC, Chang CF. Giovanella BC. Demonstration of an altered S-adenosylmethionine synthetase in human malignant tumors xenografted into athymic nude mice. J Natl Cancer Inst. 1980; 64(5): 1071-1075.

[8] Liau MC, Zhuang P, Chiou GCY. Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Clin Oncol Cancer Res. 2010; 7(2): 86-96.

[9] Liau MC, Szopa M, Burzynski B, Burzynski SR. Chemo-surveillance: A novel concept of the natural defense mechanism against cancer. Drugs Exptl Clin Res. 1989; 13(Suppl. 1): 72-82.

[10] Liau MC, Baker LL. The functionality of chemo-surveillance dictates the success of wound healing as well as cancer therapy. Nov Res Sci. 2021; 7(2): 1-3.

[11] Liau MC, Craig CL. Chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer evolution and to cure cancer. In: New Horizones in Medicine and Medical Research. 2022: Vol 6, Chapter 3. Print ISBN: 978-93-5547-607-4.

[12] Liau MC. Lee SS, Burzynski SR. Hypomethylation of nucleic acids: A key to the induction of terminal differentiation. Intl J Exptl Clin Chemother. 1989; 2: 187-199.

[13] Liau MC, Craig CL. On the mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy. Intl Res J Oncol. 2021; 5(3): 25-31.

[14] Liau MC, Baker LL. Wound healing, evolution of cancer and war on cancer. Intl Res J Oncol. 2021; 4(3): 13-20.

[15] Liau MC, Craig CL. No scar as an indication of perfect wound healing, ugly scar as imperfect wound healing and cancer as failed wound healing. J Cancer Tumor Intl. 2022; 12(1): 29-34.

[16] Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes: Nature's way to eradicate cancer stem cells. Online J Complement Alt Med. 2019; 2: 1-6.

[17] Liau MC, Craig CL, Liau LL. Abnormal methylation enzymes as the most critical issue of cancer. Intl Res J Oncol. 2023; 6(2): 168-176.

[18] Liau MC, Craig CL, Baker LL. Restoration of chemo-surveillance as the top priority to save cancer patients. Intl Res J Oncol. 2023; 6(2): 227-237.

[19] Kamparath BN, Liau MC, Burzynski B, Burzynski SR. Ptotective effect of Antineoplaston A10 in hepatocarcinogenesis induced by aflatoxin B_1. Intl J Tiss React. 1990; 12 (Supple): 43-50.

[20] Liau MC. A perfect cancer drug must be able to take out both cancer cells and cancer stem cells, and to restore the functionality of chemo-surveillance. 3rd Intl Conference on Medicinal Chemistry and Drug Design. 2021; 13.

[21] Liau MC, Craig CL, Baker LL. Destabilization of abnormal methylation enzymes as the only viable option for the elimination of cancer stem cells to save cancer patients. Intl Res J Oncol. 2024; 7(1): 142-152.

[22] Jordan CT, Guzman ML, Noble M. Cancer stem cells. N Engl J Med. 2006; 355: 1253-1261.

[23] Sengupta A, Cancelas JA. Cancer stem cells: A stride toward cancer cure? J Cell Physiol. 2010; 225: 7-14.

[24] Abbazadeqan MR, Bagheri V, Razavi MS. Isolation, identification and characterization of cancer stem cells: A review. J Cell Physiol. 2017; 232: 2008-2018.

[25] Zhang M, Atkinson RL, Rosen JM. Selective targeting of radiation resistant tumor initiating cells. Proc Natl Acad Sci USA. 2010; 107(8): 3522-3527.

[26] Moitra K, Lou H, Dean M. Multidrug efflug pumps and cancer stem cells: Insight into therapy resistance and therapeutic development. Clin Pharmacol Ther. 2011; 89(4): 491d-502.

[27] Frame FM, Maitland NJ. Cancer stem cells, model of study and implication of therapy resistance mechanisms. Adv Exp Med Biol. 2011; 720(2): 105-118.

[28] Liau MC, Fruehauf JP. The winner of the contest to eradicate cancer stem cells win the contest of cancer therapies: The winner is cell differentiation agent formulations. Adv Complement Alt Med. 2020; 5: 476-478.

[29] Liau MC, Craig CL, Baker LL. CDA formulations as the only option capable of reducing cancer mortality. Intl J Res Oncol. 2024; 3(2): 1-11.

[30] Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes to combat cancer: The nature's choice to win the war on cancer. Lambert Academic Publishing. 2020; ISBN: 978-620-2-66889-7.

[31] Liau MC, Baker LL. Destruction promotes the proliferation of progenitor stem cell and cancer stem cells. Therefore, non-destruction strategy is a better choice for cancer therapy. J Pharmacol Pharmaceu Phharmacovigi. 2020; 4: 029. https://doi.org/10.24966/PPP-5649/100029

[32] Liau MC, Craig CL, Baker LL. Wound healing process as the most appropriate modality of cancer therapy. Eur J Applied Sci. 2023; 11(1): 463-471.

[33] Liau MC, Craig CL, Baker LL. CDA formulations as persuasive good cancer drugs to save cancer patients. Intl J Clin Oncol Cancer Res. 2024; 9(1): 15-24.

[34] Liau MC. Pharmaceutical composition inducing cancer cell differentiation and the use for treatment and prevention of cancer thereof. US Patent. 2007; 7232578.B2.

[35] Liau MC, Fruehauf PA, Zheng ZH, Fruehauf JP. Development of synthetic cell differentiation agent formulations for the prevention and therapy of cancer via targeting of cancer stem cells. Cancer Stud Ther J. 2019: 1-15.

[36] Liau MC, Kim JH, Fruehauf JP. In pursuance of differentiation inducers to combat cancer via targeting of abnormal methylation enzymes. J Cancer Tumor Intl. 2020; 10(2): 39-47.

[37] Liau MC, Kim JH, Fruehauf JP. Arachidonic acid and its metabolites as the surveillance differentiation inducers to protect healthy people from becoming cancer patients. Clin Pharmacol Toxicol Res. 2021; 4(1): 7-10.

[38] Liau MC, Huang LJ, Lee JH, Chen SC, Kuo SC. Development of differentiation helper inducers for the differentiation therapy of cancer. Chin Pharm J. 1998; 50(5): 289-303.

[39] Liau MC, Liau CP. Methyltransferase inhibitors as excellent differentiation helper inducers for differentiation therapy. Bull Chin Cancer. 2002; 11: 166-168.

[40] Liau MC, Kim JH, Fruehauf JP. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. J Pharmacol Pharmeceu Pharmavovigi. 2019; 3: 9. https://doi.org/10.24966/PPP-5649/100009

[41] Huang M, Ye Y, Chen S, Chai JR, Wang ZY. Use of all-trans retinoic acid in the treatment of promyelocytic leukemia. Blood; 1988: 72: 567-572.

[42] Le Cjutre P, Mologui L, Cleris L, et al. In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor. J Natl Cancer Inst. 1999; 91: 163-168.

[43] Williamson PJ, Kruger AR, Reynolds PJ, Hamlin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndromes. Br J Haemato. 1994; 87(4): 743-745.

[44] Boula A, Vougarelis M, Giammouli S, Katrinakis G, Psyllaki M, Pontikoglou C, et al. Effect of CA2 of antitumor necrosis factor-alpha antibody therapy on hematopoiesis of patients with nyelodysplastic syndromes. Clin Cancer Res. 2006; 12(10): 3099-3108.

[45] Liau MC, Craig CL, Baker LL. Exceptional allosteric regulation of methylation enzymes. In: Saraydin SU (ed), Novel Research Aspects in Medicine and Medical Research. 2023; Vol 4: 39-56. https://doi.org/10.9734/bpi/nramms/v4/19881D

[46] Counter CM, Gupta J, Harley CB, Lever B. Telomerase activity in normal leukocytes and hematological malignancies. Blood. 1995; 85(9): 2314-2320.

[47] Fu C, Chen Z. Telomerase activities in myelodysplastic syndromes. Chin Med J (Eng). 2002; 115(10): 1475-1478.

[48] Woll PS, Kjallquist U, Chowdhury O, Doolittle H, Wedge DC, Thongjuea S, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. Cancer Cell. 2014; 25(6): 794-808.

[49] Ma J. Differentiation therapy of malignant tumor and leukemia. CSCO Treaties on the Education of Clinical Oncology. 2007; 480-486.

[50] Santi DV, Norment A, Garret CE. Covalent bond formation between a DNA-cytosine methyl-transferase of DNA containing 5-azacytosine. Proc Natl Acad Sci USA. 1984; 81(22): 6993-6997.

[51] Palii SS, van Emburgh BO, Sankpal UP, Brown KD, Robertson KD. DNA methylation inhibitor 5-aza-2'-deoxycytidine induces reversible DNA damage that is distinctly influenced by DNA-methyltransferase 1 and 3B. Mol Cell Biol. 2008; 28(2): 752-771.

[52] Kezietepe T, Hideshima T, Catley L, Raje N, Yasui H, Shiraishi N, et al. 5-Azacytidine, a methyltransferase inhibitor, induces ATR-mediated DNA-double strand break response, spoptosis, and synergistic cytotoxicity with doxorubicine and bortezomib against multiple myeloma cells. Mol Cancer Ther. 2007; 6(6): 1718-1727.

[53] Yang Q, Wu F, Wang F, Cai K, ZhangY, Sun Q, et al. Impact of DNA methyltransferase inhibitor 5-azacytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and homeostasis of gene expression in vitro. J Cell Biochem. 2019; 120(10): 17459-17471.

[54] Prassana P, Shack S, Wilson VI, Samid D. Phenylacetate in chemoprevention of 5-aza-2'-deoxycitidine-induced carcinogenesis. Clin Cancer Res. 1995; 1(18): 865-871.

[55] Caudet F, Hodgson JG, Eden A, Jackson-Grusby L, Dausman J, Gray JW, et al. Induction of tumor in mice by genomic hypomethylation. Science. 2003; 300(5618): 489-492.

[56] Feng F, Li W, Ling CQ, Zhang Y, Gin F, Wang H, et al. Phase III clinical trials of the cell differentiation agent-2 (CDA-2): Therapeutic efficacy on breast cancer, non-small cell lung cancer and primary hepatoma. Chin J Clin Oncol. 2005; 2(4): 706-716.

[57] Bourgead MF, Beassancon F. Induction of 2'5'-oligoadenylate synthetase by retinoic acid in two transformed human cell lines. Cancer Res. 1984; 44: 5355-5360.

[58] Hwa J, Martin K. Chapter 18. The eicosanoids: prostaglandins, thromboxanes, and related compounds. In: Katzung BG (ed), Basic and Cliniocal Pharmacology (14th ed), New York, NY. McGrow-Hill Eduction, 2017.

[59] Ho ATV, Palla AR, Blake MR, Yual ND, Wang YX, Magnusson KEG, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem function, augmenting regeneration and strength. Proc. Natl Acad Sci. USA. 2017; 114(26): 6675-6684.

[60] Riciotti E, FitzGerald GA. Prostaglandins and inflammation. Arteroscler Thromb Vascu Biol. 2011; 31(5): 986-1000.

[61] Morley JE. Hormone, aging and endocrine in the elderly. In: Lelig P, Frohman LA. Endocrinology and metabolism, 4th (edn), McGrow-Hill, Inc., Medical Publishing Division, New York, 2001; 1455-1482.

[62] Liau MC, Szopa M, Burzynski B, Burzynski SR. Quantitative assay of plasma and urinary peptides as an aid for the evaluation of patients undergoing Antineoplaston therapy. Drugs Exptl Clin Res. 1987; 13(Supple. 1): 61-70.