Restoration of Chemo-surveillance as a Top Priorityto Save Cancer Patients

ABSTRACT

Cancer mortality is very high and is still increasing. The objective of this study is to rely on the restoration of chemo-surveillance to reduce cancer mortality called for by President Biden in his cancermoonshot initiative speech last year. The reason cancer mortality remains so high is because we are not pursuing the right approach on cancer therapy. Cancer is caused by wound unhealing due to the collapse of chemo-surveillance. Chemo-surveillance is the nature's creation of allosteric regulation to keep cells with abnormal methylation enzymes (MEs) under control. Wound healing comes naturally, because the nature creates chemo-surveillance to ensure perfection of wound healing. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). Efficient differentiation of PSCs is a critical mechanism of wound healing. MEs play an essential role on the regulation of cell replication and differentiation. In telomerase expressing cells, MEs are associated with telomerase to alter kinetic properties of MEs and the regulation in favor of cell growth, which is important for wound healing. Chemo-surveillance is an important safety mechanism to avoid unnecessary build up of cells with abnormal MEs to cause clinical symptoms such as tissue fibrosis, dementia, organ failure and cancer. Chemo-surveillance can be destroyed under pathological conditions producing elevated tumor necrosis factor (TNF) to cause cachexia symptoms resulting in the collapse of chemo-surveillance. PSCs are then forced to evolve into cancer stem cells (CSCs) by a single hit to silence TET-1 enzyme to escape contact inhibition which limits the extent of PSCs to build up.Inability of CSCs to undergo terminal differentiation due to the collapse of chemo-surveillance eventually forces CSCs to progress to faster growing cancer cells (CCs) through chromosomal abnormalities such as translocations or deletions to activate oncogenes or to inactivate suppressor genes to become full blown cancer. Obviously, collapse of chemo-surveillance is a critical event in the development of cancer, restoration of chemo-surveillance is, therefore, an easy and effective solution to save cancer patients.

Keywords:allosteric regulation; chemo-surveillance; cancer therapy; CSCs; PSCs; wound healing.

1. INTRODUCTION

Cancer mortality remains at historical high.According to NCI experts, the cancer incidence was 18.1 million and the cancer mortality was 9.5 million worldwide in 2018. which were on the way to increasewith an annual increment of 5% [1].The cancer incidence and mortality of USA were also on the way to increase. According to the American Cancer Society's statistics, during the

three years period from 2019 t0 2022, the cancer mortality increased from 1.76 million to 1.90 million with an annual increment of 2.7%,whereas the cancer mortality increased from 0.607 million to 0.609million with an annual increment of 0.1%. Obviously, cancer therapies in practice are unable to bring down cancer mortality.Cancer therapies based on the killing of CCs are the choice of cancer establishments in the pastto combat cancer, which have been drilled through as a presidential project during 1971-1976, but failed to achieve the goal to put cancer away [2]. Despite the failure, cancer establishments were trapped on the failing strategy of killing CCsto combat cancer, although they did make attempts to modify the killing of CCs by more specific approaches such asgene and targeted therapies,anti-angiogenesis agents, and immunotherapeutic agents [3].The modification of killing strategies may reduce adverse effects, but does not help to reduce mortality. Cancer therapies based on the killing of CCs are not a good choice, because such therapies can only benefit the minority of early stage cancer patients whose chemo-surveillance has not yetbeenfatally damaged, whereas the majority of advanced cancer patients whose chemo-surveillance has been fatally damagedcannot be saved by such therapies [4].That is why cancer mortality remains so high.

Cancer is caused by wound unhealing due to the collapse of chemo-surveillance, which is an allosteric regulation the nature created to ensure perfection of wound healing [5-9].Human body produces metabolites active as differentiation inducers (DIs) which are chemicals capable of eliminating telomerase from abnormal MEs, and differentiation helper inducers (DHIs) which are inhibitors of MEs capable of potentiating the activity of DIs[5, 10, 11]. DIs and DHIs function as allosteric regulators to destabilize abnormal MEs to achieve induction of terminal differentiation of PSCs, which is a critical mechanism of woundhealing [12].Chemo-surveillance was our creation to describethe surveillance role of DIs and DHIs to eliminate cells with abnormal MEs [5].Cancer development and wound healing are remarkably similar. Carcinogen or wound initiates the damage to trigger a cascade of responsesto cause the replication and the terminal differentiation of PSCs in order to heal the wound.MEs are at the center of theseevents, which play an essential role to regulate replication and differentiation of PSCs [9]. The functionality of chemo-surveillancedictates the success of wound healingto avoid disastrous consequences of wound unhealing.Wound healing is a simple matter that comes naturallywithout having to put up any effort, because of the functioning of chemo-surveillance. Cancer therapy should also be a simple matter if the functionality of chemo-surveillance can be restored to that of healthy people [13-15].Cell differentiation agent (CDA)formulationsare preparations made up by DIs and DHIs that can quickly replenish the depleted CDA of cancer patients to help control of the build up of cells with abnormal MEs. Evidently, CDA formulations are the best drugs to eliminate PSCs and CSCs, since these drugs are the partnersof these cells to carry out theirbiological mission on wound healing. The elimination of CSCs is far more important than the elimination of CCsto account for the success of cancer therapy, since most fatal effects of cancer are the making of CSCs such as metastasis, recurrence, drug resistance and angiogenesis[16-18].

2. COMMENTARIES AND DISCUSSIONS

2.1 Abnormal MEs as the Most critical Issue of Cancer

Perpetual proliferation is the most outstanding feature of cancer. The blockade of differentiation, and the activation oncogenesand/or the inactivation of suppressor genes are responsible for the perpetual proliferation of cancer cells.The blockade of differentiation is caused by abnormal MEs which is the most critical issue of cancer, but attracts very little attention. Abnormal MEsare due to the association of MEswith telomerase [19], which happens on PSCs, the precursors of CSCsin the preneoplastic state, and carries on to CSCs and CCs, whereas oncogenes and suppressors genes emerge quite late in the cancer development.Abnormal MEs area single eventshared by all cancers [20], whereas oncogenes and suppressor genes involved in the pathogenesis of different cancers are multiple.A stroke to eliminate abnormal MEs can cure all cancers, that includesthe elimination of chromosomal abnormalities [9,13, 16-18, 21-31], whereas the correction of a particular gene abnormality can only slow down the replication of cancer cells displaying such specific abnormality.One chromosomal abnormality may be solved to slow down the replication of cancer cells for a while, but there may soon pop up another chromosomal abnormality to negate the therapeutic effect achieved. Development of unresponsiveness is common to targeted therapies[30].Therapy to target on abnormal MEs can offer a permanent cure, because cancer cells all become terminally differentiated cells unable to recover the ability to replicate.Obviously, abnormal MEs are the most critical issue of cancer [31].Therapies based on killing of CCs do not have to take into consideration what are more important to contribute to the development of cancer. Killing of CCs can wipe out all issues involved.The problems of cancer therapies based on killing of CCs are the contribution to damage chemo-surveillance and the inability to take out CSCs which are protected by drug resistance and anti-apoptosis mechanisms [14, 15, 29].

Why is abnormal MEs the most critical issue of cancer? Because MEs play an essential role on the regulation of cell replication and differentiation and cancer arises as a consequence of cell differentiation becoming faulty. Because of important biological role onthe regulation of cell replication and differentiation, MEs are subject to exceptional allosteric regulations [9,31]. Allosteric regulation is an important biological regulatory mechanism for the maintenance biological optimum to avoid extreme often to display clinical symptoms. Most important enzymes involved in the regulation of biological process are subject to allosteric regulation. MEs are exceptional to subject to double allosteric regulations, one on the individual enzymes and another on the enzyme complex. MEs are essential for the regulation of cell replication and differentiation by virtue of the fact that DNA methylation controls the expression of tissue specific gene [32], and pre-rRNA methylation controls the production of ribosome [33], whjichin turn dictates the commitment of cell to initiate cell replication [34]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [35].MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)- methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH)[36].On the individual enzymes, SAHH is the receptor of steroid hormone or related allosteric regulators.SAHH is an unstable enzyme which requires a stabilizing factor such as steroid hormone or related allosteric regulators to assume a stable configuration to form dimeric enzyme complex with MTand this dimeric enzyme complex is then in a position to form a termary enzyme complexwith MAT.Steroid hormone or related

allosteric regulators dictate the optimum of cell growth and function. In telomerase expressing cells, MEs are associated with telomerase [19]. The association of MEs with telomerase changes kinetic properties of MAT-SAHH isozyme pair and the regulation to tiltin favor of cell replication.K_m values of the telomerase associated isozyme pair are 7-fold higher than the normal isozyme pair. The increased K_m values are an indication that cells with abnormal MEs have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy).A larger pool sizeof AdoMet and AdoHcy isimportant for the promotion of the growth of cells with abnormal MEs. It has been shown by Prudova et al. [37] that AdoMet could protect protein from protease digestion. Chiba et el. [38] found that pool sizes of AdoMet and AdoHcu shrunk greatly when HL-60 cells were induced to undergo terminal differentiation. Obviously, abnormal MEs play an important role for the build up of cells with abnormal MEs.Abnormal MEs do not seem to cause problems for normal stem cells such as embryonic stem cells (ESCs) and PSCs which express telomerase. There are safety mechanisms such as contact inhibition to restrict the build up of normal stem cells with abnormal MEs , TET-1 enzyme to by pass the blockade of differentiation byabnormal MEs [23, 24]and chemo-surveillance to destabilize abnormal MEs [5-7]. Problems may arise when these safety mechanisms become dysfunctionalto display clinical symptomssuch as tissue fibrosis, dementia, organ failure and cancer [8, 14, 15, 39].The protection of chemo-surveillance is particularly important to avoid disastrous consequences of wound unhealing.

2.2 Chemo-surveillance as an Allosteric Regulation to Avoid Pathological Build Up of Cells with Abnormal MEs

Wound healing is an extremely important biological issue, so that the mature creates chemo-surveillance as an allosteric regulation to ensure perfection of wound healing to avoid pathological build up of cells with abnormal MEs. Because of the nature's creation of chemo-surveillance, wounds are always healed without having to put up any effort. Take surgical wounds for example, treatments with suture and antibiotics are subsidiary to speed up and to prevent infection. So, wound healing really is a simple matter. Cancer arises due to the failure to heal wound[40]. When an animal was challenged with a hepatocarcinogen, the host liver was actively engaged in the repair of damages created by the hepatocarcinogen manifested asnumerous tiny preneoplastic hyperplastic nodulewhich display abnormal MEs.These nodules must represent an active proliferation of PSCs in the process of wound healing. Most of these preneoplastic hyperplastic nodules disappeared, suggesting completion of wound healing. Only a few larger sized carcinomas appeared later, obviously from unhealed tiny hyperplastic nodules. If the animal was given Antineoplaston A10 during the challenge with hepatocarcinogen, hepatocarcinogenesis process could be effectively prevented [42]. Antineoplaston A10 is phenylacetylglutamine which was effective as an anti-cachexia agent to reverse the excessive urinary excretion of low molecular weight metabolites often associated with cancer patients [5]. It appears that the protection of the functionality of chemo-surveillance is good enough to ensure completion of wound healing created by hepatocarcinogen to prevent carcinogenesis.The administration of Antineoplaston A10 alone was also effective to cure earlystage cancer [5]. The effectiveness of Antineoplastone A10 in the chemoprevention of carcinogenesis and in the therapy of cancer is attributable to its effect to

protect and to restore the functionality of chemo-surveillance.Antineoplaston A10 was ineffective to affect growth of cancer cells even at very high concentrations.The effective chemicals are metabolites of wound healingproduced by animals or human body.

We knew that human body generated metabolites with DIs and DHIs [5, 10, 11]. DIs and DHIs are hydrophobic metabolites that can be retained by C18 and recovered by 80% methanol. Peptides share the chemical properties of DIs and DHIs. Therefore, peptides can serve as surrogate molecules to represent DIs and DHIs content of the plasma and urine.Quantitative assays of plasma and urinary peptide, based on peptide/ml plasma over peptide/mg creatinine, revealed that healthy people could maintain a steady plasma/urine ratio around 0.8.Assigning the plasma/urine peptide ratio around 0.8 as the cell differentiation agent (CDA) with a level of 5. The distribution of 108 cancer patients in percentages among CDA levels of 5:4:3:2:1:0.5 were 1.8:6.5:16.7:35.2:22.2:19.6 [43]. CDA levels reflect the status of cancer patients very well. The higher the level the healthier the patients. Evidently, the progression of the disease causes CDA level to drop, and the administration of cytotoxic drugs accelerates the decline of CDA levels.CDA at the level 3 is probably the critical level to determine the effectiveness of therapies with cytotoxic agents. Above CDA3, cancer patients may have the chance to restore chemo-surveillance to subdue surviving CSCs, whereas below CDA3, the chance for the restoration of chemo-surveillance to combat surviving CSCsis almost none.Cytotoxic therapies can only benefit the minority of early stage cancer patients, whereas the majority of advanced cancer patients with CDA level below 3 cannot benefit from cytotoxic therapies. All cancer patients can benefit from therapy with Antineoplaston, which can elevate CDA levels..Patients treated with Antineoplaston if responding well, CDA level would increase to approach that of healthy people. If not, CDA level continued to decline [43].Antineoplastons are preparations of natural wound healing metabolites. Fast growing cancers are known to express a high level of degradation enzymes to salvage starting substrates for macromolecular syntheses in order to support their fast growth. Natural wound healing metabolites may be degraded in faster growing cancer cells to lose effectiveness. For the elimination of faster growing CCs, it may be necessary to employ non-natural DIs and DHIs to bypass degradative enzymes. Two sets of CDA formulations may be necessary to achieve effective therapy of cancer. One set CDA-CSC is made by natural DIs and DHIs to target CSC, and another set CDA-CC is made by non-natural DIs and DHIs to target faster growing CCs[15]. A combination therapy relying on CDA-CSC to target CSCs and cytotoxic agents or immunological agents to target CCs may also be effective forcancer therapy [27, 29].Our studies clearly indicate that canceris caused by the collapse of chemo-surveillance. Therefore, a top priority to save cancer patients is to restore the functionality of chemo-surveillance.When the functionality of chemo-surveillance is restored to the level of CDA5 as the healthy people, the therapy of cancer will be as easy as wound healingrequiring no effort.

2.3 Screening for Suitable Cancer Drugs in Myelodysplastic Syndrome

Cancer is caused due to the failure to heal wound [40]. Wound healing requires the proliferation and the terminal differentiation of PSCs [12]. Wound triggers biological and immunological responses [44]. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins

(PGs)which aregood for wound healing. Although PGs are excellent DIs[45],their function at the initial stage of wound is believed to create edema for the extravasation of inhibitors such as DIs and DHIs in order for PSCs to proliferate. The final stage of wound healing is accomplished by chemo-surveillance, the nature's creation of allosteric regulation to destabilize abnormal MEs. The immunological response of the wound prompts the production of TNF which isbad for wound healing. TNF is responsible for cachexia symptoms to cause the collapse of chemo-surveillance to heal wound. The failure to heal wound forces PSCs to evolve into CSCs.

The development of MDS follows exactly the wound healing course. MDS often starts with a display of an immunological disorder [46] which prompts the production of inflammatory cytokines. Among these cytokines, TNF is the critical factor related to the development of MDS, because antibody to TNF was effective to halt the progression of MDS [47]. TNF causes excessive apoptosis of bone marrowstem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, and neutrophils. TNF is also responsible for cachexia symptoms commonly shared by inflammatory patients and cancer patients. A characteristic disorder of cachexia is the excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [4849]. As a consequence, chemo-surveillance normally operating in healthy people to keep cells with abnormal MEs in check becomes dysfunctional to heal wound, thus allowing PSCs to evolve into CSCs. The propagating pathological cells have been identified as CSCs [50].Thus, MDS is a disease attributable entirely to CSCs.

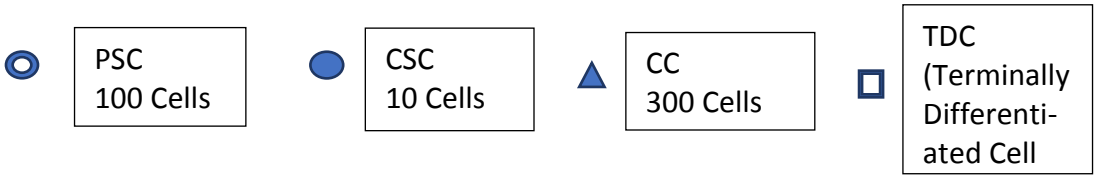
Therapy of MDS requires terminal differentiation of pathological CSCs to become functional erythrocytes that is exactly the critical mechanism of wound healingrequiring the terminal differentiation of PSCs. Killing of CSCs cannot cure MDS. Besides, killing of CSCs cannot be easily done, because these cells are protected by drug resistance and anti-apoptosis mechanisms. Elimination of CSCs is very important for cancer therapy, because these cells contribute most of fatal effects of cancer such as metastasis, recurrence, drug resistance and angiogenesis. Evidently, CDA formulations made up by DIs and DHIs are the best drugs to eliminate CSCs. So far vidaza, decitabine and CDA-2 were the three drugs approved for the therapy of MDS in China. Vidaza and decitabine were also approved for the therapy of MDS in the USA. CDA-2 was our creation which was a preparation of wound healing metabolites purified from freshly collected urine by reverse phase chromatography employing XAD-16 as the adsorbant[22].CDA-2 has all wound healing elements as Antineoplastons except peptides which are not retained by XAD-16.CDA-2 inactivates abnormal MEs through DIs and DHIs as allosteric regulators, whereas vidaza and decitabine inactivate abnormal MEs through covalent bond formation between methyltransferase and 5-azacytosine base incorporated into DNAfrom vidaza or decitabine[51].According to Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology who was instrumental to conduct clinical trials for the approval of the three MDS drugs in China, findings based on two cycles of clinical trial protocol each cycle 14 days, showedCDA-2 had a slightly better therapeutic efficacy based on cytological evaluation, and a marked better therapeutic efficacy based on hematological improvement evaluation, meaning patients were no longer dependent onblood transfusion to stay healthy [52]. Better yet, CDA-2 was devoid of severe adverse effects, whereas vidaza and decitabine were known

carcinogens[53, 54] and very toxic to DNA [55-57]. Obviously, CDA-2 is the drug of choice for the therapy of MDS with better therapeutic efficacy and devoid of adverse effects. CDA-2, vidaza and decitabine are the three drugs to pass the Litmus test of MDS as the right cancer drugs.Most drugs approved for cancer therapy cannot pass the Litmus test of MDSas the right cancer drugs.Evidently, elimination of CSCs is the most important criterion for the effective therapy of cancer. Drugs to inactivate abnormal MEs are the best drugs to eliminate CSCs. Destabilization of abnormal MEsthrough DIs and DHIs as the nature's creation of allosteric regulation is the best approach of cancer therapy.

2.4 Restoration of Chemo-surveillance as a Top Priority to Save Cancer Patients

The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19th century [58]. It was again brought up by Dvorak in 1986 [59]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [60].We provided the most important details on this subject that included abnormal MEs to block differentiation [19, 20,61]; chemo-surveillance as the nature's creation of allosteric regulati0on to ensure perfection of wound healing [3,5-8]; DIs and DHIs as wound healing metabolites and also as active players of chemo-surveillance [10, 11]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [62]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [3, 12, 15, 40]; and the evolution of CSCs from PSCs due to wound unhealing [23, 24, 63, 64]. These studies very convincingly establish that cancer arises as a consequence of wound unhealing, and the most critical event is the collapse of chemo-surveillance. Thus, the restoration of chemo-surveillance is a top priority to save cancer patients.Chemo-surveillance is the nature's creation to prevent pathological build up of cells with abnormal MEs. It is the most effective strategy to eliminate CSCs, the most troubling elements of cancer cells to contributeto fatal effects of cancer. In fact the contribution to cause the damage to chemo-surveillance and the ineffectiveness on CSCs are responsible for the failure of cytotoxic agents to put cancer away [2, 4, 8, 13-18,23, 24. 65]. Once CSCs can be effectively under control by restoring CDA to the healthy level 5 of healthy people, curing of cancer can be as easy as healing wound.Elimination of CCs is, of course, an important issue of cancer. After all, CCs constitute the major part ofcancer mass. But Elimination of CCscannot bring down cancer mortality [1].Elimination of CSCs can bring down cancer mortality. The most important matter is to approve CDA formulations to restore chemo-surveillance to put away problems contributed by CSCs. Approval of CDA formulations takes 10 years of clinical trials. It will be 10 years we canbegin to see the drop of cancer mortality, if cancer establishments are willing to accept CDDA formulations as the right cancer drugs.

A summary drawing to show restoration of chemo-surveillance through CDA formulations to save cancer patients vs cytotoxic agents to cause cancer mortality is presented in the following Figure-1.



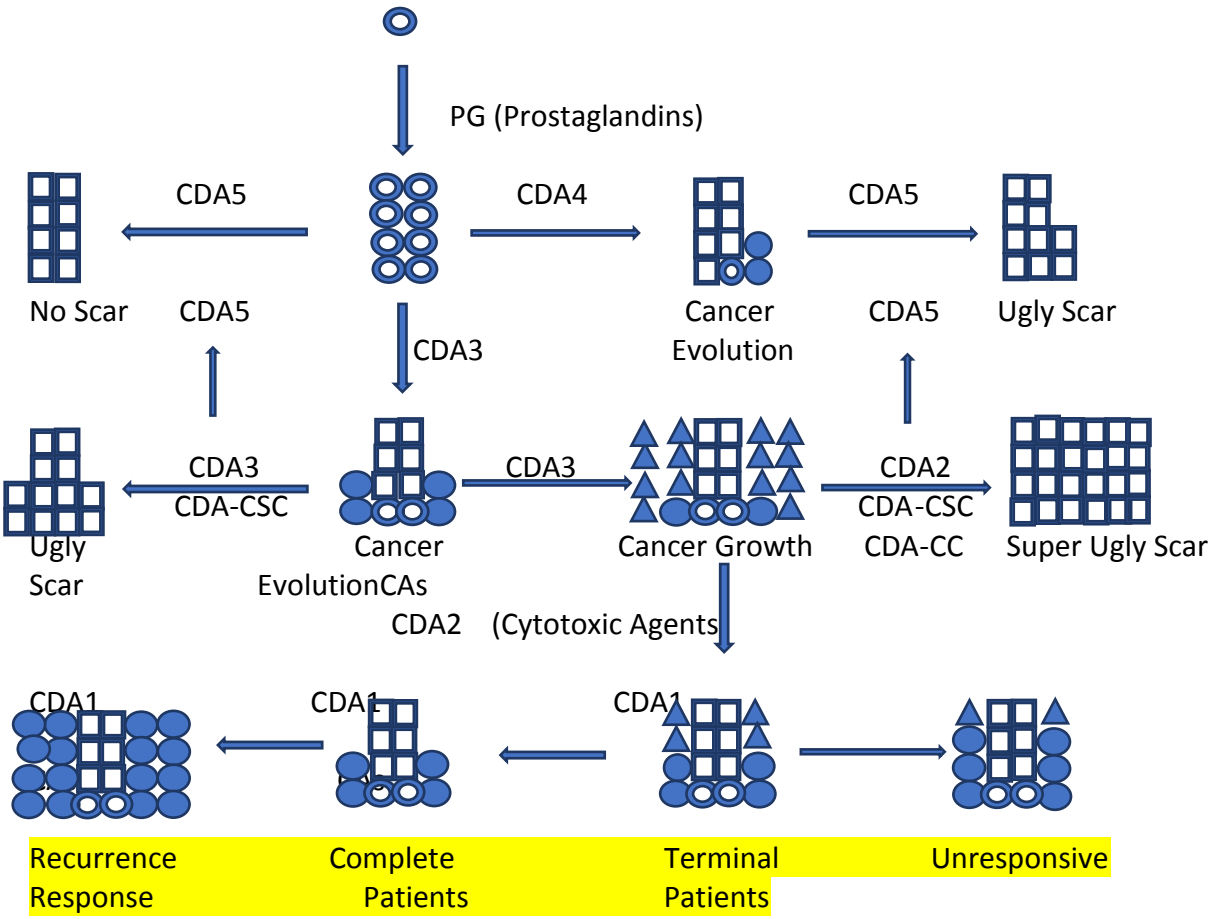


Figure 1. Restoration of chemo-surveillance through CDA formulations to save cancer patients vs cytotoxic agents to cause cancer fatality.

CDA5 depicts chemo-surveillance at the level of health people, and CDA4-1 depict at lower levels due to the collapse of chemo-surveillance. CAs include cytotoxic chemotherapeutic agents, radiation, apoptosis inducing agents and immunological therapeutic agents. The progression of cancer is a factor to cause the collapse of chemo-surveillance, and the application of cytotoxic agents accelerates thecollapse of chemo-surveillance. CDA-CSC is a CDA formulation made up by natural DI+DHI such as ED_{50} of arachidonic acid+2x$RI_{0.5}$ of pregnenolone and CDA-CC is a CDA formulation made up by unnatural DI+DHIsuch as ED_{50} of BIBR 1532+2x$RI_{0.5}$ of pyrvinium pamoate [15]. Administration of CDA formulations can restore chemo-surveillance to assist cancer therapy no matter how badly chemo-surveillance has been damaged. Cytotoxic agents contribute to the damage of chemo-surveillance. Only early stage cancer patients whose chemo-surveillance has not yet fatally damaged can benefit from cytotoxic therapy, relying on the restoration of chemo-surveillance to subdue surviving CSCs

which are not responsive to cytotoxic agents. Advance cancer patients whose chemo-surveillance has been fatally damaged become unresponsive or fortunately still responsive to reach complete response are ultimately succumb to recurrence.

3. CONCLUSION

Cancer is caused by wound unhealing due to the collapse of chemo-surveillance, which is the nature's creation of allosteric regulation to prevent the pathological build up of cells with abnormal MEs.MEs play an important role on cell replication and differentiation. Because of this important biological role, MEs are subject to exceptional double allosteric regulations, one on the individual enzymes and another on the enzyme complex.MEs are a ternary enzyme complex consisting of MAT-MT-SAHH. On individual enzymes, SAHH is the receptor of steroid hormones or related allosteric regulators which dictate the optimum of growth and differentiation. In telomerase expressing cells, MEs are subject to another allosteric regulation involving telomerase and chemo-surveillance. Telomerase tilts the regulation in favor of cell growth. Cell growth is an important mechanism for the development of fetus and wound healing, because ESCs and PSCs express telomerase.There are safety mechanisms to limit the build up of normal stem cells such as contact inhibition, TET-1 enzyme to undergo lineage transitions and chemo-surveillance to keep abnormal MEs under control. When such safety mechanisms become dysfunctional, PSCs are forced to evolve into CSCs and then progressed to faster growing CCs, which are an effort to heal the wound.Obviously, chemo-surveillance plays a very important role to limit the build up of cells with abnormal MEs, the restoration of this important mechanism is at most important to save cancer patients.

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