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Innovating Metastatic Cancer Treatment Protocol

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Cancer treatment is complex, and current possibilities for patients depend on the cancer type and stage, in addition to the age, sex, and overall health of the patient. We've seen some important changes in cancer treatment in the past decade. Improved diagnostics and new treatments can gain precious time for patients. But for people living with metastatic breast cancer, the constant threat of relapse, of the cancer spreading and progressing, is an unwelcome reality.

Cancer metastasizes due to several factors, namely attack by the immune system, lack of oxygen and necessary nutrients, large amounts of lactic acid produced by glycolysis and increased cell death.

Therefore, the majority of the presently available treatments for cancer also bear the potential to induce metastasis. A holistic perspective of cancer metastasis:

Metastasis - predetermined or acquired genetic trait Cloud Integration in Healthcare

Suzuki and Tarin suggested that metastasis is an acquired trait, based on the significant differences in the gene expression profile between primary and lymph node metastatic breast cancer observed through microarrays. The prevailing theory of cancer is that it all begins with a single or even a series of genetic mutations. If metastasis is a trait of cancer, then it must also share the same origin. However, when considering cellular growth and development in the embryonic stage of any organism, a number of

embryonic cells, such as primordial germ cells and neurocrest cells, naturally migrate over long distances to their final location, without any genetic mutations.

Necrosis and Apoptosis are associated with metastasis

Necrosis is crucial for the diagnosis of malignancy. In diagnostic pathology, the presence and extent of necrosis are important references for the diagnosis of malignancy. Although there is no proven explanation for the cause of necrosis, the most plausible explanation is that the tumor overgrows the ability of the circulatory system to supply sufficient nutrients.

In fact, extensive necrosis is a common indicator of metastasis. For example, axillary lymph node metastasis was detected in a case of intracapsular carcinoma of the mammary gland. This type of lesion is usually considered as in situ carcinoma, which is rarely associated with metastasis. The strong association of tumor necrosis with metastasis indicates that cell death per se or a factor closely associated with cell death, such as lack of blood supply, is a strong stimulator of cancer metastasis

The increased apoptosis associated with poor clinical outcome is not merely attributed to the fast growth of cancer. In fact, it appears reasonable to hypothesize that, under conditions of increased cell death, surviving cells are likely to move away. An inhibitor of the inhibitor of apoptosis protein, which was designed for the treatment of cancer through inducing apoptosis, was found to facilitate the metastasis of breast cancer cells to bone tissues. Should this hypothesis prove to be correct, a number of studies are expected to be published reporting similar findings, particularly since several drugs that induce apoptosis are currently in the stage of clinical trial.

Immune reaction/inflammation stimulates metastasis

The association between immune reaction and cancer is an interesting paradox. Inflammation, which is an immune reaction, is widely accepted as a facilitator of carcinogenesis and cancer metastasis.

'Immune escape' has been described as a hallmark of cancer by Hanahan and Weinberg. In fact, escape from attack is a natural response in the biosphere rather than the patent of cancer cells. The immune escape techniques used by cancer cells include down regulation of the expression of major histocompatibility complex molecules, by which cancer cells try to become invisible to immune cells. The other important strategy is escape. It has been demonstrated that macrophages and other immunocytes promote cancer cell metastasis . Therefore, I agree with Prehn and Prehn that immunosuppression may be a better approach to treating cancer compared with immunostimulation.

Warburg effect and metastasis

The predilection of cancer cells to engage in a high rate of glycolysis, even under conditions of adequate oxygen supply, is referred to as the Warburg effect and was first described by the famous German biochemist Otto Warburg in 1924. Approximately 90 years after its discovery, the Warburg effect has again attracted significant attention in the field of cancer research. A number of researchers suggest that glycolysis renders cancer cells superior to their normal peers regarding proliferation.

However, glycolysis produces large amounts of lactic acid, thereby significantly increasing the acidity of the surrounding environment. Therefore, cancer cells tend to move away from this hostile environment. It was previously demonstrated that low local pH stimulated cancer invasion and metastasis; by neutralizing the acidic pH, the occurrence of invasion and metastasis was reduced.

Promotion of blood circulation vs. Metastasis

In traditional Chinese medicine, the cause of cancer was considered to be 'blood stasis' so to enhance the efficacy of radiotherapy, based on the hypothesis that increased blood flow provides more oxygen to the tissues, which is critical for radiotherapy. Indeed, the efficacy of radiotherapy was significantly increased but the metastasis rate was also increased. If promotion of blood circulation was used alone, it would not have triggered cancer cell metastasis.

Current Treatment Protocol

The major problem in the current types of therapies is limited efficacy as well as cytotoxicity to the normal tissues and organs leading to drug-resistant and relapsed tumor growth. These are usually successful during the early stages of cancer, but its efficacy depends on the drug administration scheme and the physiological condition of the patient e.g. Chemotherapy is not specific to cancer cells; it causes several undesirable side effects like damage to normal tissues and organs. However, the most important aspect of conventional chemotherapy is that in a significant number of cases, cancer cells develop resistance mechanisms that enable tumor progression and metastasis.

Treatment Gaps

In a survey by advocacy group Metastatic Breast Cancer (MBC) Alliance, patients expressed frustration at the "trial-and-error" nature of treatment.They also want treatments with less toxicity.

Therefore, one of the key challenges in drug discovery is demising the toxicity of chemotherapeutic agents and developing more effective and efficient drugs to improve treatments, recovery times, and overall patient quality of life.

Identification of drugs that are able to target the cancer cells without having toxic effects to normal cells would be the real responsive innovation to address the real needs of patients, including quality of life.

Innovating Treatment Protocol:

The strategic need is to look at alternative medicines and forms of treatment protocols for the effective treatment with minimizing or eliminating side effects for curative treatment.

I would propose to restructure the treatment protocol using technological frontiers and the looking at alternatives forms of medicinal treatments along with the current forms, while minimizing avoiding the usage of radiotherapy & chemotherapy in the treatment of Metastatic Cancers.

Innovating is nothing but looking afresh at the problem with a different perspective to an alternate form or tools of treatment or an combination of them for the benefit of the patient and his well being.

Prognostic Testing:

Biological clues that can help predict how a patient might respond to a medicine. The prognosis plays a central role in medical decision making, and is also valuable to patients in making decisions about aspects of their lives unrelated to their medical care. Providing prognostic information is a medico–legal responsibility.

There are several reasons why prognostic factors are important. First, by determining which variables are prognostic of outcomes we gain insights on the biology and natural history of the disease.

Second, appropriate treatment strategies may be optimized based on the prognostic factors of an individual patient.

The most important prognostic factor in all human cancers is the stage at presentation, which is the anatomic extent of the disease.

Once the identification has been undertaken then is to take a fresh view on natural compounds especially the selective acetogenins and their potential as anticancer agents.

Selective Acetogenins as Anticancer Agents

Nature represents a still largely unexplored source of bio-active molecules with a therapeutic potential. Many of these compounds have already been characterized for their multiple anticancer activities. Many of them are absorbed with the diet and therefore possess a known profile in terms of tolerability and bio-availability compared to newly synthesized chemical compounds. The discovery of important cross-

talks between mediators of the most therapeutically targeted aberrancies in cancer (i.e., cell proliferation, survival, and migration) and the metabolic machinery allows to predict the possibility that many anticancer activities ascribed to a number of natural compounds may be due, in part, to their ability of modulating metabolic pathways. Annonacin promotes selective cancer cell death via NKA-dependent and SERCA-dependent pathways

Acetogenins:

The acetogenins are known to be very potent cytotoxic compounds. The annonaceous acetogenins (AAs) are secondary metabolites found in the Annonaceae family, which are plants employed in traditional medicine for the treatment of cancer and various other diseases. These polyketides are inhibitors of Complex I in the respiratory chain of tumor cells, a process that is closely related to tumor metabolism, cell death, apoptosis, and autophagy. AAs are cytotoxic compounds that can induce apoptosis, cell cycle arrest, and autophagy in vitro, in addition to exhibiting tumor growth inhibition in vivo. The functional group related to their antineoplastic activity is suggested to be the mono or bis tetrahydrofuran ring accompanied by two or more hydroxy groups.

The versatility of the AA bioactivity therefore renders them potential therapeutic agents for cancer treatment due to the following reasons:

1. The AAs are secondary metabolites produced by the Annonaceae family. A. Squamosa is used in India for the treatment of various conditions including malignant tumors (Savithramma et al., 2011). Furthermore, A. Muricata is a popular medicinal remedy in America, Africa, and India for the treatment of cancer (Moghadamtousi et al., 2015a), while in Mexico, A. Macroprophyllata, A. Muricata, and A. Purpurea are used for the treatment of skin tumors and gastric cancer (Alonso-Castro et al., 2011; Brindis et al., 2013). The evidence indicates the AAs are molecules with significant bio-active potential.

2. Acetogenins are molecules with great potential for future cancer therapy. Their most prominent biologic activity is inhibition of the mitochondrial Complex I due to their bis-THF structure. Indeed, it was previously reported that the mono-THF AAs bearing an alkyl chain that links the lactone moiety with the THF group are noncompetitive inhibitors of Complex I (i.e., NADH: ubiquinone oxidoreductase) in the respiratory chain, which leads to a blockade of phosphorylative oxidation and a subsequent decrease in ATP production (Tormo et al., 1999; Chen et al., 2012). Such inhibition involves a large group of pathways that can induce cell death, including apoptosis and autophagy, or act in other metabolic networks as inhibitors of the lactate dehydrogenase A enzyme, as an antioxidant, or by arresting the cell cycle. Moreover, A. Muricata (Moghadamtousi et al., 2015a) and A. Squamosa L. (Chen et al., 2012a; Chen et al., 2012b; Chen et al., 2012c; Chen et al., 2016) have been reported to have cytotoxic activity against several human or other mammal cancer cell lines.

3. Apoptosis is a natural strategy of cell death that kills unnecessary or damaged cells. The main genes involved in this process are p53 and the bcl2 family; the former is a tumor suppressor, while the later could be either proapoptotic (BAD, BAX and BAK among others) or antiapoptotic (bcl2, and bcl-x) (Okada and Mak, 2004).

4. The primary function of p53 is to prevent the replication of cells with DNA damage. Therefore, p53 is inactive, and the damaged cells continue to grow and replicate DNA mutations, resulting in diseases such as cancer (Igney and Krammer, 2002; Okada and Mak, 2004). Thus, research carried out to date can be classed into two main topics: apoptosis induction or apoptosis resistance mechanisms.

5. Current apoptosis-inducing chemotherapies cause severe secondary effects on patients. The AA annonacin promotes apoptosis in cancer cells by activating the caspase 3 and Bax pathways (Yuan et al., 2003), while squamocin induces apoptosis through the expression of the proapoptotic genes Bax and Bad, which results in the cleavage of PARP and the enhanced activity of caspase 3 in bladder T24 cancer cells (Yuan et al., 2006). This contrasts with previous results where Squamocin did not induce apoptosis in breast cancer cells but inhibited proliferation by blocking the cell cycle in the G1 phase (Raynaud et al., 1999).

6. The methanol extract of A. Reticulata inhibits the expression of caspases 6 and 9 in colon and liver cancer cells (Mondal et al., 2007), while the organic and aqueous extracts of A. Squamosa down-regulate the expression of Bcl-2 in MCF-7 breast cancer cells and K-562 leukemia cells, indicating their effect as apoptosis inducers (Pardhasaradhi et al., 2005). In addition, the leaf extract of A. Muricata induces the expression of caspases 3 and 9 and inhibits cell proliferation by reducing phospho-ERK and phospho-AKT in MIA PaCa-2 cells (Yiallouris et al., 2018).

7. The AAs also lead to cycle arrest, which has implications for the proliferation of tumor cells. AAs regulate the cell cycle in the G1/S transition by inhibiting cyclin D1 expression in human hepatocellular carcinoma cells (Qian et al., 2015). In this context, the A. Muricata extract arrests the cell cycle at the G1 phase and decreases the number of cells in the S phase in a concentration-dependent manner by reducing the expression of cyclin D1, an important regulatory protein of the cell cycle (Torres et al., 2012). A similar result was observed for Squamocin, which arrests cells in the G1 phase in T24 bladder cancer cells (Yuan et al., 2006). Despite the relevance of the cell cycle, few studies have addressed how AAs affect this mechanism.

8. Aerobic Glycolysis, a mechanism used by tumor cells to obtain energy in the absence of oxygen (Figueroa-González et al., 2016; García-Castillo et al., 2017), is also a target of AAs. Various proteins and glycolytic enzymes are upregulated by HIF-1, an important transcription factor involved in tumor aerobic glycolysis, in cancer cells. Interestingly, the A. Muricata extract lowered the expression of HIF-1α and NF-κB and the levels of the glucose transporter GLUT1 and the HKII and LDHA enzymes in pancreatic cancer cells (Torres et al., 2012). In addition, the leaf extract of A. Muricata showed

antiproliferative effects in cancer cell lines and promoted cell death by the inhibition of the NKA and SERCA pumps (Yiallouris et al., 2018).

Conclusion:

Acetogenins are versatile anticancer molecules causing tumor cell death by different mechanisms. They can modulate the exclusion of chemotherapeutics drugs out of cancer cells and are strong apoptosis inducers. Their bioactive flexibility is reflected in their ability to regulate the cell cycle by arresting cells in phase G1, promoting apoptosis by the inhibition of various proteins, and even induce autophagy. Moreover, their metabolic interactions, specifically related to the transcription factors HIF1 and STAT3 and its repercussions in energy consumption, angiogenesis, inflammation, and metastasis, stand out. The anti tumor activity of AAs in vivo is promising (bullatacin, laherradurin, and cherimolin-2 are examples).

Thus we can innovate our treatment mode using prognostic testing and developing drugs based on Acetogenin derivatives on whom large clinical trials data is available today for formulating the drugs for different metastatic cancer treatment protocol, while avoiding or minimizing the use of Chemo or radio therapies.