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# Cancer Metastases and Clinical Therapies

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## Abstract

More than 90% cancer deaths are caused by cancer metastasis. As cancer metastasis is the main cause of human deaths, we shall pay more attentions on it. Currently, treatment and chemotherapy are focused on primary tumors rather than metastatic processes. Antimetastatic drugs are often used as assistant therapy. So cancer patients' survivals have been improved very little. To change this mindset, we highlight this problem by giving new perspectives and try to improve the outcome of chemotherapy of cancer patients from different possible ways. Human cancer metastasis is a long-evolving, multi-steps process that can only be treated or controlled by drugs or immuno-modulators by now. Human neoplasm metastasis, at least a month-long course, encompasses several different substages and affects or being affected by numerous genes and molecules. We have found that each drug or immuno-modulator might act differently within the various stages of a metastatic course. We, therefore, suggest that future antimetastatic therapy should be strategically optimized according to characteristics of metastatic processes in order to reach maximum therapeutic benefits. In this view, we propose, address and support this issue by using past literature evidence, our experimentations and existing biological, anatomical and pathologic characteristics.

There have been two most difficult problems in cancer chemotherapy, neoplasm metastasis and multi-drug-resistances (MDR). Among these two thorny problems, treatments of neoplasm metastasis are especially difficulty and should be placed on the highest agenda of the highest for its deadliest pathogenesis features and unpredictability of therapeutic outcome at the stage of drug initiation. Also, metastasized tumors often concomitantly manifest the characters of MDR. More than 90% cancer deaths are caused by cancer metastasis. As cancer metastases are the main cause of human deaths, we shall pay more attentions on them. Previously, treatment and chemotherapy are focused on primary tumors. Antimetastatic drugs are often used as assistant therapy. So cancer patients' survivals have been improved very little. Now there seems basically no better option other than drugs for antimetastatic treatments, however failure happening in most of clinical cases. So any small breakthrough in this respect will lead to great clinical achievements in cancer therapies [1]. Thus we reiterate we shall focus more attentions on development of more useful antimetastatic drugs and treatment of neoplasm metastases according to clinical circumstance of patients. In order to reach this goal, we propose, address and support this idea by using past literature evidence, our experimentations and existing biological, anatomical and pathologic characteristics.

## Present Clinical Antimetastatic Therapy

Present antimetastatic treatments are overwhelmed with researches and applications of antivascular (angiogenesis) and matrix metalloproteinase (MMPs) inhibitors and more than 500 related-agents of different chemical formulae have been literally reported. Currently all FDA licensed or internationally available antimetastatic drugs are generally consisted with these two types [2-5]. However, these drugs are far from satisfactory in clinics for the reasons of indiscriminative molecular inhibitions and generally low survival benefits for patients. Paradoxically to our efforts and expectations, except some antibodies, no obvious improvements and therapeutic benefits by conventional antimetastatic drugs (usually antivascular agents or MMPs inhibitors) have been achieved until now. Therapeutic benefits in late-staged or aged cancer patients are especially poor and useless [6-7]. More important, some unfavorable evidence against angiogenesis inhibitors to metastasis has been reported [8-10]. Clinical anticancer drug therapies currently in use have been mainly focusing on primary tumor growth rather than specifically targeting pathologic courses of metastases relevantly. Finding important drugs targeting specifically to neoplasm metastases is essential and indispensable [1, 11-13]. It nevertheless needs changing our focus from targeting vascularity and MMPs into more metastatic-relating molecules. So how to optimistically use drugs in antimetastatic treatments remains to be a great challenge.

## Shall Antimetastatic Drugs Offer to All Cancer Patients?

Cancer metastases do not occur in all patients. 60% patients suffer those tumor types with low metastatic rates [14]. These patients will have good survival expectancy. To those patients, there is no need of additional antimetastatic therapy. Only operations or therapy targeting primary tumors are enough. However, in many cases, we cannot know if a specific individual will metastasize or not? Or we have already found metastasized tumors when patients are diagnosed with cancer. There are two main types of options we can choose; (i) find out if some metastatic gene signatures in primary tumors [11,15,16]; (ii) treatment of metastatic foci with high active drugs. This is the central problem discussing in the following sectors (Table 1).

### Shall human tumor metastasis be treated according to clinical situations?

Present antimetastatic therapy regards patients equally. No specific attentions are paid according to clinical situations of patients. Tumor metastases involve a fixed course of pathophysiological processes [11,17,18]. Human cancer metastasis encompasses several different substages (1) invade locally through surrounding extracellular matrix (ECM) and stromal cell layers, (2) intravasate into the lumina of blood vessels; (3) tumor cells survive the rigors of transport through the vasculature; (4) arrest at distant organ sites; (5) tumor cell extravasate

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into the parenchyma of distant tissues; (6) initially survive in these foreign microenvironments in order to form micrometastases, and (7) reinitiate their proliferative programs at distant sites, thereby generating macroscopic, clinically detectable neoplastic growths [11, 17-21]. From this pathologic point of view, since a metastasis must travel more than one body-organ, the obvious different anatomic organs may possibly trigger different molecules and pathways linking neoplasm metastases. This reasonably results in being affected or inhibited with different types of drugs in different stage (Table 2). In return, different anticancer drugs will certainly not act in the same in all metastatic organs [17,18].

We previously hypothesize that many anticancer or antimetastatic drugs might act differently in these different courses of substages and could be wisely applied of drugs according to metastatic cascade. Bisdioxopiperazine compounds (Biz), including ICRF-154, Razoxane (ICRF-159, Raz), ICRF-186 and ICRF-187 (two stereo-isomers of Raz) and ICRF-193, developed in the UK, has been a series of serendipitous agents found to be significantly effective against a model of spontaneous metastasis (Lewis lung carcinoma, 3LL) [22,23]. Ever since their development (1969), new analogs Probimane and Bimolane were synthesized at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China [24]. In order to testify this hypothesis, we carried out an experiment by comparing the different drug inhibitions against a spontaneous metastatic model, Lewis lung carcinoma (3LL), which contains all processes of human metastasis cascade. Our work showed that Pro and Bim significantly inhibited the pulmonary metastasis of 3LL both following day2 and day8 injections, but Raz only significantly inhibited the pulmonary metastasis of 3LL following day2 injections. Pro inhibited the pulmonary metastasis of 3LL more potently than Bim did at equitoxic dosage. Comparatively, it seems that Pro has superior inhibition of pulmonary metastasis of 3LL than Bim and Raz for its exclusive targeting potentiality [17].

From the report of James et al, the detachment of 3LL began at day 6-8 [25]. Our study supports that Raz only is highly effective against tumor detachments yet ineffective against the formed metastatic foci. This data can be used to explain also why Raz was reported to be more effective against neoplasm metastases for spontaneous metastatic tumors rather than for artificial ones [3]. However, Pro and Bim might be equally effective in both d2 and d8 treatment schedules. From our early data of $^{14}$C-probimane tracing and autoradiography [26], an obvious greater accumulation of Pro was found in metastatic tissues.It can help to explain that Pro can more effectively inhibition of neoplasm metastasis than Raz in formed metastatic foci through stronger antiproliferative effect [27].

| Compounds types | Proposed targets |
|---|---|
| Sia analogues or conjugates | Pathologic sias |
| DNA chelating agents | DNA template |
| Sialyltransferase inhibitors | Sia adding or releasing from antigens |
| Vaccines | Human immune system |
| Antibodies | Pathologic antigens |
| Antimetastatic agents | Unknown mechanism |
| **Sia-anticancer drugs** | Tumor affinity molecules |

**Table 1:** Different pathways of antimetastatic drugs targeting neoplasm sialic acids [32].

| Methods | Utilizations |
|---|---|
| New drug target screen | Antimetastatic drug developments |
| Drug administrate or schedule analysis | Treatments with high efficiency |
| Mechanistic study of antimetastatic drugs | Better use of antimetastatic drugs |
| Diagnostic studies | Find out if a patient need antimetastatic drugs |
| Metastatic cascade study | Properly use antimetastatic therapy |
| New active antimetastatic drugs | Formed metastatic foci and tumors |

**Table 2:** Roadmap to perfect clinical antimetastatic therapy.

In general, we propose that the MMPs inhibitors might be more active in preventing tumor cells from detaching from primary locations. Immuno-modulators might promote the activity of macrophages in killing tumor cells during the vascular and lymphatic circulations [28,29]. Angiogenesis inhibitors might be used as the substage of attaching of tumor cells to remote organs and micrometastasis formation. However, highly cytotoxicity agents might be more effective in treatment of formed metastatic foci and preference-organs [18].

### Find more metastatic-related molecules

Current antimetastatic therapies rely heavily on angiogenesis or MMPs inhibitor. Since tumor metastasis is so complex a process that triggers more than 100 molecules, other metastatic-related molecules such as sialic acids [30-36] might be also very useful in antimetastatic therapy. We need to strengthen these researches.

Sialic acids (Sias, neuraminic acid) are a special series of 9-carbon backbone acidic carbohydrates and typically found at outermost part of sugar chains attached to cell membrane macromolecules. They play many important roles in a series of physiological and pathologic processes, including microbe binding that leads to infections, regulation of the immune response, the progression and spread of human malignancies and in certain aspects of human evolution. The earliest work tackling the phenomenon of a positive relationship between sias and tumors can be traced back to Kimura et al from 1958. Their discovery is tumor cells might excrete and contain more sialyl glycoproteins or glycolipids. These characteristic later have been found to link with highly metastatic tumor types [16]. It has been shown that there are higher sias contents in highly metastatic tumor cell lines than those in lower metastatic tumor cell lines. Since then, numerous similar reports and reviews have been published rapidly. Many researchers have also showed patients with tumors of high levels of sialyl Lewis X or sialyl Tn antigens appear to be linked with poor prognosis of patients which is one of the most conspicuous pathologic features of sias in tumors clinically. Many relationships between neoplasm metastasis and sia aberration can be seen from references and I shall not reemphasized them here. These pathways should be regarded as an important target for drug therapies [30-33]. Other new drug targets are also given [34-37].

To conclude, the decision of antimetastatic treatment should be better based on the stage of a metastasis in patients. It might broaden present customs of finding antimetastatic drugs only into clinical drug option strategy as a complementary and perfection of individualized cancer chemotherapy [38,39].

## Concluding Remarks

Since tumor metastasis is the main cause of cancer patients and current clinical therapeutic options are unsatisfactory, thus we need to pay more attentions on these researches and update our ideas on this matter. Since the population of cancer patients is so large, if we adhere these researches and any improvements in metastatic therapy will save tremendous life. Let's hope the best.

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