New Insights into Individualized Antimetastatic Therapy

Da-Yong Lu1*, Ting-Ren Lu2 and Hong-Ying Wu2
1School of Life Sciences, Shanghai University, Shanghai 200444, PR China
2College of Science, Shanghai University, Shanghai 200444, PR China

Abstract

More than 90% of cancer deaths are caused by cancer metastasis. Since cancer metastasis is the main cause of human deaths, antimetastatic treatment should be decisive factor for patients’ survival. Current cancer chemotherapy is mainly targeted on primary tumors and late stage patients’ survival has improved very little. It is suggested to improve the outcome of chemotherapy of cancer patients from different possible ways; e.g. to make more efforts to manufacture new types of antimetastatic drugs and optimize use of antimetastatic drugs in clinics. This review will describe how to optimized use of antimetastatic drugs in clinics.

Keywords: Neoplasm metastases; Cancer chemotherapy; Cancer treatment; Cancer pathology; Cancer pharmacology; Cancer medicinal chemistry

90% of cancer patients die of cancer metastasis. However, currently cancer chemotherapies are mainly focusing anticancer drugs targeting primary tumor instead of metastatic foci. So although the primary tumors have been inhibited by antiproliferative drugs, patient’s survival has been increased very little. If we shall change our focus on development of effective antimetastatic drugs and pursue of individualized cancer chemotherapy targeting metastatic pathogenesis stages. Thus we might expect enhancing patients’ survival by individualized antimetastatic therapies in future [1,2]. Now there seems basically no better option other than drugs for antimetastatic treatments, yet cancer metastasis treatment commonly does not work in most cases in clinics. Any small breakthrough for antimetastatic therapy will lead to great clinical achievements in cancer therapies [3]. Thus herein it is reiterated that more attentions should be paid to development of more effective antimetastatic drugs and treatment of neoplasm metastases according to clinical circumstance of patients. In order to achieve this goal, we address individualized antimetastatic therapy by targeting different metastatic cascade and drugs targeting at formed metastatic foci.

Should Antimetastatic Therapy be Different from Antiproliferative Therapy?

Shall antimetastatic therapy be different from antiproliferative therapy [4]? It has been found that the hallmarks of cancer [5] are somewhat different from the hallmarks of metastasis [6]. The hallmarks of cancer are those genes that decide the unlimited growths of cancer cells. However, the hallmarks of metastasis are those genes that decide the interactions between tumor cells and environments (human bodies). They are different type of genes and drugs. However, current clinical chemotherapies only provides antiproliferative agents to cancer patients and most of patients (90%) die of neoplasm metastasis. Only if some effective wide-spectrum antimetastatic drugs are found or using individualized antimetastatic therapy, cancer patients’ survival can increase dramatically.

Drawbacks of 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 most FDA licensed or internationally available antimetastatic drugs have been categorized as these two types [7-11]. However, due to indiscriminate molecular inhibitions and generally low survival benefits for patients, these drugs are far from satisfactory in clinics. 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. Therapeutic benefits in late-staged or aged cancer patients are especially poor and useless [12,13]. More importantly, some unfavorable side-effects of these inhibitors in humans have been reported. Also, phase III MMPs inhibitor studies showed that there are no therapeutic benefits of MMPs inhibitors for cancer metastasis in terms of patient survival [12-15]. The pathogenic processes of neoplasm metastases involve complications and are time consuming [1,2]. Angiogenesis and MMPs are only parts of them. Clinical antimetastatic drug therapies should change our focus to develop new antimetastatic drugs or target different stages of metastatic cascades [2,16,17].

Should Human Tumor Metastasis be Treated According to Clinical Situations?

Present antimetastatic therapy treats patients equally. No specific attentions are paid according to clinical situations of patients [2,16,17].

Tumor metastases involve a fixed course of pathophysiological processes. 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 vascularity; (4) arrest at distant organ sites; (5) tumor cells extravasate 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 [1,2,18-21]. From this pathologic point of view, since a metastasis must travel more than one body-organ, the obvious different anatomic organs may possibly

Corresponding author: Da Yong Lu, School of Life Sciences, Shanghai University, Shanghai 200444, PR China. E-mail: ludayong@sh163.net; ludayong@shu.edu.cn

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trigger different molecules and pathways linking neoplasm metastases. This reasonably results in being affected or inhibited with different types of drugs in different stages of metastatic processes. In return, different anticancer drugs will certainly not act in the same way in all metastatic organs.

Previously it is hypothesized that many anticancer or antimetastatic drugs might act differently in these different courses of substages and could be wisely applied according to metastatic cascade [16,17].

In general, it was proposed that the MMPs inhibitors might be more active in preventing tumor cells from detaching primary locations [15]. When cancer cells enter to blood or lymphatic vessels, only 1/1,000,000,000-5,000,000,000 cells will survive [22]. Human’s immuno-system destroys most of cancer cells. Immuno-modulators might promote the activity of macrophages in killing tumor cells during the vascular and lymphatic circulations [23,24]. 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 the treatment of formed metastatic foci and preference-organs [2,16,17].

This type of antimetastatic therapy can be regarded as individualized antimetastatic therapy-giving antimetastatic drugs according to metastatic cascade (Figure 1).

Find More Metastatic-Related Molecules

Current antimetastatic therapies heavily rely on angiogenesis or MMP inhibitors. Since tumor metastasis is so complex a process that triggers more than 100 molecules, other metastatic-related molecules, such as sialic acids [25-28] might be also very useful in antimetastatic therapy. These researches need to be boosted (Table 1).

Other new types of drug targets are also given in references [29-40]. They are cell-signal inhibitors, AMF, HGF/c-Met, TGF-β inhibitors, β-catenin inhibitors [36], and cell movement inhibitors [40]. These metastatic-related targets and inhibitors have not been licensed but have a great potential for future clinical uses. The more these targets are studied, the more useful drugs could be expected (Table 2).

Targeting the Formed Metastatic Foci in Clinics

Most people die of cancer with formed metastatic cancer. In these patients, MMPs inhibitors or antivascular agents do not work all the time. Thus, high active drugs targeting to these metastatic tumors need to be developed. Recently, it is known that transmission of primary tumor to metastatic tumor in body is parallel to the transmission of epithelial to mesenchymal [41,42]. Thus it might be mechanistically different between drugs targeting primary tumors and formed metastatic tumor. In formed metastatic tumor tissues, LY2157299 [2] or probimane [16,43,44] or apoptotic agents [45] might be better active. In future, these types of researches will be boosted.

Presently, the best way of antimetastatic drugs targeting formed metastatic foci is to combine cytotoxic anticancer drugs with therapeutic antibodies [46-54]. But the cost of antibodies is high. In future, we shall design and develop more effective and less cost antimetastatic drugs.

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 [55-58].

References


