Advanced Techniques in Biology & Medicine

ISSN: 2379-1764

Lu et al., Adv Tech Biol Med 2013, 1:1
DOI: 10.4172/2379-1764.1000106

Review Article Open Access

New Insights into Individualized Antimetastatic Therapy

Da-Yong Lu[1]*, Ting-Ren Lu[2] and Hong-Ying Wu[2]

[1]School of Life Sciences, Shanghai University, Shanghai 200444, PR China
[2]College 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.

Shall 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 chemotherapy 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 indiscriminative 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 vasculature; (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

Received April 07, 2013; **Accepted** April 23, 2013; **Published** April 26, 2013

Citation: Lu DY, Lu TR, Wu HY (2013) New Insights into Individualized Antimetastatic Therapy. Adv Tech Biol Med 1: 106. doi:10.4172/2379-1764.1000106

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 useable 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

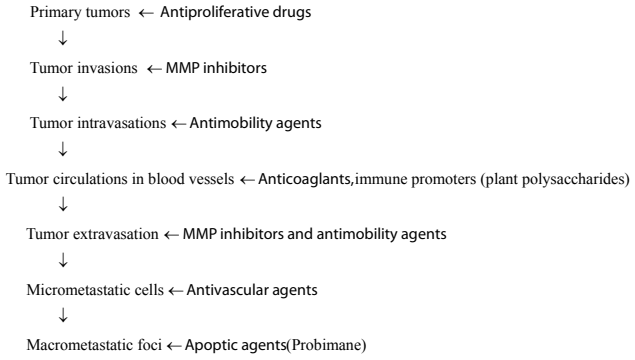

Figure 1: Proposed strategy of using antimetastatic agents in clinics.

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 anti-metastatic drugs targeting neoplasm sialic acids.

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

Table 2: Roadmap to perfect clinical antimetastatic therapy.

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

1. Lu DY, Lu TR, Cao S (2012) Cancer metastases and clinical therapies. Cell Dev Biol 1: e110.
2. Valastyan S, Weinberg RA (2011) Tumor metastasis: molecular insights and evolving paradigms. Cell 147: 275-292.
3. Lu DY, Lu TR (2010) Antimetastatic activities and mechanisms of bisdioxopiperazine compounds. Anti-Cancer Agent Medicinal Chemistry 10: 564-570.
4. Mina LA, Sledge GW Jr. (2011) Rethinking the metastatic cascade as a therapeutic target. Nat Rev Clin Oncol 8: 325-332.
5. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100: 57-70.
6. Gupta GP, Massague J (2006) Cancer metastasis: building a framework. Cell 127: 679-695.
7. Sava G, Bergamo A (1999) Drug control of solid tumour metastases: a critical view. Anticancer Res 19: 1117-1124.
8. Kessenbrock K, Plaks V (2010) Werb Z Matrix metallopoteinases: regulator of the tumor microenvironment. Cell 141: 52-67.
9. Taraboletti G, Margosio B (2001) Antiangiogenic and antivascular therapy for cancer. Current Opinion in Pharmacology 1: 378-384.
10. Folkman J (2006) Angiogenesis. Annual Rev Med 57: 1-18.
11. Lu DY, Huang M, Zhou J, Ding J (2006) Recent advances in anti-metastatic drug development. Acta Pharmacol Sin 27: 66-67.

12. Paez-Ribes M, Allen E, Hudock J, Takeda T, Okuyama H, Vinals F, et al. (2009) Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 15: 220-231.

13. Ebos JM, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, et al. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell (2009) 15: 232-239.

14. Verheul HM, Pinedo HM (2007) Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. Nature Rev Cancer 7: 475-485.

15. Coussens LM, Fingleton B, Matrisian LM (2002) Matrix metalloproteinase inhibitors and cancer: trials and tribulations. Science 295: 2387-2392.

16. Lu DY, Wu FG, Zhen ZM, Lu TR, Wu HY, et al. (2010) Different spontaneous pulmonary metastasis inhibitions against Lewis lung carcinoma in mice by bisdioxopiperazine compounds of different treatment schedules. Scientia Pharmaceutica 78: 13-20.

17. Lu DY, Xi YC (2012) Antimetastatic therapies according to metastatic cascade. Adv Pharmacoepidemiology & Drug Safety 1: e107.

18. Poste G, Fidler IJ (1980) The pathogenesis of cancer metastasis. Nature 283: 139-146.

19. Fidler IJ (1990) Critical factors in the biology of human cancer metastasis: twenty-eighth G.H.A. Clowes memorial award lecture. Cancer Res 50: 6130-6138.

20. Fidler IJ (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nature Rev Cancer 3: 453-458.

21. Klein CA (2008) The metastasis cascade. Science 321: 1785-1787.

22. Marx V. Tracking metastasis and tracking cancer. Nature 494: 131-136.

23. Fidler IJ (1985) Macrophages and metastasis--a biological approach to cancer therapy. Cancer Res 45: 4714-4726.

24. Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF (2004) Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 351: 781-791.

25. Lu DY, Cao JY (2001) Structural aberration of cellular sialic acids and their functions in cancer. J Shanghai Univ 5: 164-170.

26. Lu DY, Lu TR, Wu HY (2011) Antimetastatic therapy targeting aberrant sialylation profiles in cancer cells. Drug Therapy Studies 1, e12.

27. Lu DY, Lu TR, Wu HY (2012) Development of antimetastatic drugs by targeting tumor sialic acids. Scientia Pharmaceutica 80: 497-508.

28. Xi YC, Lu DY (2012) Relationship between tumor sialic acids and neoplasm metastasis and as a drug target. Cell Developmental Biol 1: e106.

29. Vetvicka V, Fusek M (2012) Procathepsin D as a tumor marker, anti-cancer drug or screening agent. Anticancer Agents in Medicinal Chemistry 12: 172-175.

30. Chen L, Yang S, Jakoncic J, Zhang JJ, Huang XY (2010) Migrastatin analogues target fascin to block tumour metastasis. Nature 464: 1062-1066.

31. Valastyan S, Reinhardt F, Benaich N, Calogrias D, Szasz AM, et al. (2009) A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. Cell 137: 1032-1046.

32. Lu da Y, Chen XL, Ding J (2007) Treatment of solid tumors and metastases by fibrinogen-targeted anticancer drug therapy. Medicinal Hypotheses 68: 188-193.

33. Bobek V (2012) Anticoagulant and fibrinolytic drugs - possible agents in treatment of lung cancer? Anticancer Agents in Medicinal Chemistry 12: 580-588.

34. Rothwell P, Fowkes FG, Belch JF, Ogawa H, Warlow CP, et al. (2011) Effect of daily aspirin on long-tem risk of death due to cancer: analysis of individual patient data from randomized trials. Lancet 377: 31-41.

35. Nash GF, Turner LF, Scully MF, Kakkar AK (2002) Platelets and cancer. Lancet Oncol 3: 425-430.

36. Iiizumi M, Liu W, Pai SK, Furuta E, Watabe K (2008) Drug development against metastasis-related genes and their pathways: a rationale for cancer therapy. BBA 1786: 87-104.

37. Lu DY, Lu DR, Ding J (2010) Cell biological manifestations of bisdioxopiperazines treatment of human tumor cell lines in culture. Anti-cancer Agents Med Chem 10: 657-660.

38. Goodman SL, Picard M (2012) Integrins as therapeutic targets. Trends Pharmacol Sci 33: 405-412.

39. Paredes J, Figueiredo J, Albergaria A, Oliveira P, Carvalho J, et al. (2012) Epithelial E- and P-cadherinss: role and clinical significance in cancer. BBA 1826: 297-311.

40. Bendas G, Borsig L (2012) Cancer cell adhesion and metastasis: selectins, integrins, and the inhibitory potential of heparins. Int J Cell Biology 676-731.

41. Thiery JP, Acloque H, Huang RYJ, Nieto MA (2009) Epithelial-mesenchymal transitions in development and disease. Cell 139- 871-890.

42. Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. J Clin Invest 119: 1420-1428.

43. Lu DY, Huang M, Xu CH, Zhu H, Xu B, et al. (2006) Medicinal chemistry of probimane and MST-16: comparison of anticancer effects between bisdioxopiperazines. Medicinal Chemistry 2: 369-375.

44. Lu DY, Lu TR (2010) Anticancer activities and mechanisms of bisdioxopiperazine compounds probimane and MST-16. Anti-cancer Agent Medicinal Chemistry 10: 78-91.

45. Mehlen P, Puisieux A (2006) Metastasis: a question of life or death. Nature Rev Cancer 6: 449-458.

46. Lu DY, Lu TR, Wu HY (2013) Combination chemical agents with biological means in cancer therapy. Research and Reviews in BioScience 7: 153-155.

47. Lechleider RJ, Kaminskas E, Jiang X, Aziz R, Bullock J, et al. (2008) Ixabepilone in combination with capecitabine and as monotherapy for treatment of advanced breast cancer refractory to previous chemotherapies. Clin Cancer Res 14: 4378-4384.

48. Gillespie DL, Whang K, Ragel BT, Flynn JR, Kelly DA, et al. (2007) Silencing of hypoxia inducible factor-1alpha by RNA interference attenuates human glioma cell growth *in vivo*. Clin Cancer Res 13: 2441-2448.

49. Geyer CE, Forster J, Lindqyuist D, et al. (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355: 2733-2743.

50. Vermorken JB, Mesia R, Rivera F, et al. (2008) Platinum-based chemothgerapy plus cetuximab in head and neck cancer. N Engl J Med 359: 1116-1127.

51. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, et al. (2010) Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 363: 1812-1821.

52. The Lancet Oncology (2010) New hope for advanced gastric cancer. Lancet Oncology 11: 211.

53. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, et al. (2007) Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357: 2666-2676.

54. Jolien T, Miriam K, Annemieke C, Cees JR, Geert JMC, et al. (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 360: 564-572.

55. Lu da Y, Chen XL, Ding J (2006) Individualized cancer chemotherapy integrating drug sensitivity tests, pathological profile analysis and computational coordination - an effective strategy to improve clinical treatment.Medical Hypotheses 66: 45-51.

56. Lu DY, Lu TR, Chen XL, Ding J (2012) Individualized cancer chemotherapy. Hypotheses in Clinical Medicine. Ed, Shoja MM, Agutter PS, Tubbs RS, Ghanei M, Ghabili K, Harris A, Loukas M., chapter 13. Nova Publisher, USA.

57. Lu DY, Lu TR, Chen XL (2012) Individualized cancer chemotherapy, are we ready for that yet? Metabolomics 2: e113.

58. Lu DY, Lu TR, Cao S (2012) Individualized cancer chemotherapy by detecting cancer biomarkers? Metabolomics 2- e121.