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Antimetastatic Therapies according to Metastatic Cascade

Da-Yong Lu[1]* and Yin-Ci Xi[2]*

[1]School of Life Sciences, Shanghai University, Shanghai200444, PR China
[2]College of Food Science & Technology, Shanghai Ocean University, Shanghai201306, PR China

There have been two most difficult problems in cancer biology and therapeutics, neoplasm metastasis and multi-drug-resistances (MDR). Among these two thorny problems, treatments of neoplasm metastasis are especially difficult and should be placed on the highest agenda 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. 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].

Tumor metastases involve a fixed course of pathophysiological processes, and are responsible for more than 60% of cancer deaths worldwide [2]. Human cancer metastasis encompasses at least three main different substages (i) tumor detachment from primary location; (ii) tumor cells flow in the blood or lymphatic vessels; (iii) tumor cell attachment and penetration through blood vessels of distant organs and angiogenesis [3-4]. From this pathologic point of view, since a metastasis must travel more than one body-organ, the different anatomic organs may possibly trigger different molecules and pathways linking neoplasm metastasis [4]. This reasonably results in being affected or inhibited with different types of drugs at different stages. In return, different anticancer drugs will certainly not act in the same way in all metastatic organs [5].

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 [6-9]. Currently all FDA licensed or internationally available anti-metastatic drugs are these two types. However, these drugs are far from satisfactory in clinics for the reasons of indiscriminative molecular inhibitions and generally low survival benefits for patients. More importantly, these therapies are also not without toxicities [10]. So how to optimistically use drugs in antimetastatic treatments remains to be a great challenge.

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) [11,12]. 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 [13]. 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 [14].

From the report of James and Salsbury, the detachment of 3LL began at day 6-8 [15]. 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 [8]. However, Pro and Bim might be equally effective in both d2 and d8 treatment schedules. From our early data of 14C-probimane tracing and autoradiography [16], 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 [17].

This experimental evidence further supports our previous hypothesis that each drug or immuno-modulators might act differently within various stages of a metastatic course. 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 [18]. However, highly cytotoxicity agents might be more effective in treatment of formed metastatic foci and preference-organs. 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 [19-20].

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

Dr. Yin-Ci Xi, College of Food Science & Technology, Shanghai Ocean University, Shanghai-201306, PR, China, E-mail: xiyinci@gmail.com

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