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Anti-metastatic drug development, overview and perspectives

Abstract

Introduction: Neoplasm metastasis is a multiple-step and multi-component involved pathogenesis causing large human mortality and socioeconomic burden. Currently, anti-metastatic drugs are the widest therapeutic targets for clinical cancer trials. The most effective drugs are yet to be developed.

Methods: Anti-metastatic drugs are evaluated by a great variety of tumor models and cutting-edge biotechnology. Anti-metastatic drug evaluation and development is still a pharmaceutical challenge worldwide. Many technical deficit and knowledge limitation has been overcoming decade by decade.

Discussion: Different aspects of chemical, pathologic, pharmacological and pharmaceutical knowledge breakthroughs for neoplasm metastasis evaluation are discussed. Better knowledge for the complexity of metastasis pathology is essential for therapeutic moving forward.

Conclusion: A great therapeutic responses and benefits can be expected after aforementioned biomedical study, technical progression and drug development.

Keywords: neoplasm metastases, cancer plasticity, drug combination, metastatic cascade, personalized medicine

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Introduction

Epidemics

Cancer is the secondary number of disease-related human mortality across the world. Approaching annually 100 million global human cancer mortality is observed more recently.[1] Among this large mortality population of ancer patients, 70-90% is related with cancer metastasis.[2,3] The main therapeutic option for cancer metastasis is by drug treatment. This is led by various causalities of different cancer subtypes, molecular origin, technical deficit and organ impairment caused by metastatic progression. One of them is the deficit in drug evaluation and development.[4]

Introduction for metastatic treatment

Neoplasm metastasis is a multiple-step and multi-component involved pathogenesis that causes large human mortality and socioeconomic burdens. Once a patient develops cancer metastasis in other healthy organs, his chance of 5-year survival rate is very low (<15%). Current anti-metastatic drugs are evaluated by a great variety of tumor models and fast-growing biotechnology (simple and complex). However, the correlation between experimental data and clinical therapeutic outcome is unsatisfactory. To implement with this difficulty issue, different aspects of pathophysiologic property, pharmacological comparisons and biomedical knowledge for neoplasm metastasis should be associated and promoted.

Therapeutic convention

Neoplasm metastasis is mostly treated by drugs. No other therapeutic option had been well formed for high-quality metastatic management. As a result, high effective anti-metastatic drug targets and mechanisms were not well elucidated for most tumor subtypes.

Drug category deficiency

Overall, cancer patients' survival has hardly been improved while overt metastatic nodules are obvious in the clinic.[5] Moreover, only narrow-range of agents have been systematically compared for metastatic management activity and mechanisms. Therefore, breakthrough in drug developments can achieve beneficial outcomes in clinical cancer trials, especially survival benefits.[6–13] Previous study for experimental data and biological theories is discussed in different experimental exploration and clinical scenarios.

Therapeutic comparison

Current categories of anti-metastatic agents or drugs

A lot of anticancer or other agents, drugs and medical evidences were reported. Mounting chemical structure, pathogenesis, clinical evidence and mechanisms show anti-metastatic targeting or efficacy data in experimental or clinical studies. To promote this study, major therapeutic knowledge, chemical entities, pharmacological targets and therapeutic mechanisms are achieved and shared (Table 1).

Table 1 Major anti-metastatic targets and mechanisms

Drug categories	Molecules & pathways
Bisdioxopiperazine compounds	Tumor cell detachments[14,15]
MMP inhibitors	Microenvironments (extracellular matrix, ECM)[16]
Angiogenesis inhibitors	Tumor blood & nutrition[17,18]
Bisphosphonates or vitamin D	Bone metastasis19
Various drugs	Invasion-metastasis cascade[20,21]
Probimane & polysaccharide	Aberrant sialylation in tumors[22–26]
Immune promoters	Migration & tumor survivals[27,28]
Assistant therapy	Blood coagulants or oxidative stress[29–31]
Gut microbiota	Different tumors and metabolic syndrome[32,33]
Cancer stem cell inhibitors	Difficult to define[34–36]
Next generation	Seed and soil[28]
New generation	Cancer plasticity state[37–39]
Traditional Chinese medicine	Human body and organ functionality[40]
Cellular adhesion molecules	Cancer-environmental interaction[41]

Evaluative architecture

To compare the efficacy of different categories of anti-metastatic agents, evaluative systems and architectures should be promoted.[4] They are consisted in basic knowledge, evaluative convention, animal models, latest technology and cost-consideration. To facilitate researches of drug evaluation, systematic convention and protocols should be mandated. Correspondingly, biomedical guideline and framework should be provided. From invitation of new systems, new compounds or bio-agents may enter into clinics.

Antimetastatic drugs

Overall situation

There are a lot compounds or bio-agents that have been reported being capable to inhibit neoplasm metastasis in certain preliminary evaluative models, clinical evidence and case reports. These compounds or drugs have different molecular targets, beneficial efficacy and novel therapeutic mechanisms. They contain structures of synthetic, bio-agents or phytochemicals and pharmaceutical innovation (nanodrugs or drug carriers). We herein outline them in different therapeutic scopes and mechanisms.

Bisdioxopiperazine compounds

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, were the earliest agents against spontaneous metastasis in mice (Lewis lung carcinoma, 3LL).[15,16] Lately, new analogs Probimane and Bimolane were synthesized in China as well as MST-16 marketed in Japan.[42,43] Their roles and mechanisms were compared in the past.[42–45] Many ne mechanisms and therapeutic schedules should be found and new derivatives could be synthesized for therapeutic promotion and toxicity reduction.[46]

Tumor and microenvironment

Primary tumors are embedded in surrounding microenvironment. Tumor metastasis begins with tumor microenvironment break-down and tumor cell infiltration. Tumor cells and their surrounding matrix can interact, crosstalk and mutual-benefits that finally enter into invasion-metastasis cascade.[20,21] The matrix metalloproteinase (MMPs) inhibitors are proposed to limit tumor metastases in early stage of metastatic-cascade[17] Correspondingly, different types of MMP inhibitors play crucial roles for cell dislocation and metastatic onset.

Angiogenesis inhibitors

New blood vessels (angiogenesis) provide sufficient nutrients and oxygen in tumor growth, survival and pro-metastatic niche from primary tumor enlargements to metastatic outgrowth in distant organs. Many angiogenesis inhibitors have been developed for managing tumor growth and metastasis. Drugs (commonly synthetic chemical or antibodies against vascular growth factors) play roles of vascular inhibitions for metastatic disruption and possibly the induction of tumor apoptosis.[18,19,47,48] Several weeks or months survival benefits can be achieved by this type of therapies in the latest pathologic stages of cancer patients.

Bisphosphonates (BP) for osteosarcoma and bone metastasis treatment

Human bone is a vulnerable tissue that is easily damaged from outside pressure and metástasis-including osteosarcoma and tumor metastasis from other subtypes or sources. BP has a long history in osteoporosis alleviation and treatments. Several study reports that BP can be used for treating bone tumor and other sources of neoplasm metastases.[19] Many drug targets and underlying mechanisms should also be understood by systematic pharmacological stud and clinical cancer trials. In this kind of drug treatment, drug combination with other anticancer drugs may be promising.

Immune modulatory agents (plant extracts or phytochemicals)

Treatment of neoplasm metastases via immune-modulatory pathways and mechanisms by plant extracts or phytochemicals is widely acknowledged. Growing experimental data and clinical reports show that plant extracts (most polysaccharides and many phytochemicals) can inhibit tumor metastases in animal models.[22,23] They are suggested to enhance and regulate many immune function and responses (innate or adaptive immunity—humeral or cellular factors, components and lymphocytes) in animals and humans.

Circulating tumor cells

Tumor cells or clusters migration in vascular system (blood or lymphatic) should endure a great pressure from outside forces (physics, biological or immune modulator). This stage of tumor cells is vulnerable to outside attacks, especially different forms of human immunity responses and mechanisms. It was found that agents of immune promotion can clear great number of tumor cells floating in host vasculature (>99% of clearance of living tumor cells in blood circulation). The circulating tumor cells (mesenchymal type-rich) are different from primary tumors or metastatic colony (epithelial type-rich).[37–39] Many biological molecules or cells also play crucial roles in this metastatic process. As a result, this is a promising drug target and therapeutic pathways for metastatic spread and localization. In this diversity of inhibitory components of immune-modulation, activated macrophages are the most important one.

Cell adhesion molecules

Cell adhesion molecules (CAM), such as E-cadherin, p-cadherin, integrin, selectin, play key roles in cancer growth, migration, survival and metastasis finale. Cell-cell and cell-matrix interactions, mutual benefits and regulation totally determine the sizes, survival and capability of metastatic spread, migration, metastasis colonization and counteractive measures.[47,48] Heparin, anti-coagulants, pro-inflammatory factors and lymphocytes can mediate CAM related metastatic processes and affect therapeutic outcomes in patients with solid tumor subtypes, such as lung, breast or other cancer subtypes.[49,50] This special types of pathophysiological pathways and mechanisms may have great future.

Cancer plasticity (EMT/MET)

The adaptive phenotype of neoplasm tissue is a complex feature of cancer progression and metástasis.[51,52] It means that features of tumor cells in human bodies are changeable (epithelial-mesenchymal transition and mesenchymal-epithelial transition, EMT/MET). Past clinical evidence showed that a variation between cancer detachment (EMT) and metastatic formation in remote sites (MET).[53] This therapeutic dilemma is currently difficult to solve in pharmacological framework.[38] The therapeutic interventions against tumor plasticity can achieve great therapeutic benefits and human lifespan elongation.[37–39] We hope some effective therapeutic paradigms in this respect can be designed and discovered in the following decades.

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Mechanism study

Benefits and disadvantageous

To design and discover effective therapeutics against neoplasm metastasis, pathological insights should be based and updated. Thus, understanding towards the mechanisms of pathogenesis and therapeutics may trigger major breakthroughs to overcome neoplasm metastases. Several key mechanisms should be focused.

Three key causalities for metastatic treatment compromise

i. Dual roles of many key molecules and pathways

ii. Human immunity is complex and diversity in molecules and cell types

iii. Long course of Invasive-metastatic cascade

Dual roles of many associated molecules and pathways

Several tumor hallmarks are faced with dual properties and characters in key molecules and pathogenesis of neoplasm metastasis, like oxidative stress, multiple microenvironment components (MMPs), tissue inflammatory, different array of function and regulation of cell genetics (suppressers or promoters). At present, it is difficult to decide which roles of many biological molecules or pharmacological pathways may play in different cancer patients.

To explore these mechanisms, any single experiment or evaluation should be cautious to explain the outcomes and benefits of metastatic inhibition and disruption due to the complex character of neoplasm metastasis. New experiments and clinical approaches will be built to evaluate metastatic spread management and drug development.

The property of complex and diverse metastatic targets and mechanisms are difficult for evaluating in animal models that is crucial for drug discovery and development. As a result, metastatic-associated biomarker diagnostics and biomedical targets is a way for moving forward for drug licensing and essential for fundamental knowledge progress and management promotion.

Complex nature of human immune system

Human immune system is a complex and important discipline as equal volume as discipline of cancer researches and therapy. Its complex and significant feature represents as vast number of different immune-related cells, growth factors, cytokines and regulatory systems that provide great assistance for patient's health systems and survivals.

Human immune cells produce huge numbers of diversity of cytokines. These cells and cytokines are mutual benefits and deterioration. At this stage, we cannot fully determine what types of immune cells or cytokines can be integrally manipulated for metastatic management in different conditions. But, immune-related therapies are the foremost promising architecture for metastatic control and management in the future. Unlike chemical-based anti-metastatic drugs (cytotoxic targeting and efficacy), immunological agents (bio-agents or check-point inhibitors) are proposed to target metastatic foci in more specific-pathways. It is reasonable to believe that anti-metastatic therapies can be greatly improved from the maturity of medical science and knowledge in human immunology. Thus, we may promote these biological researches and therapeutic applications in the clinic.

Invasive-metastasis cascade

Invasive-metastatic cascade is not new for most cancer researchers and oncologists. But therapeutic option for that is not perfect in clinical metastatic trials.[20,21] Previously, only our proposal was proposed for this strategies.[21] Invasive-metastatic cascade is a mystery process for therapeutic intervention. From this pathologic point of view, different anatomic organs and cascade stages may be treated with different therapeutics (Figure1).[21] New discoveries may further support this therapeutic ideology and theory.

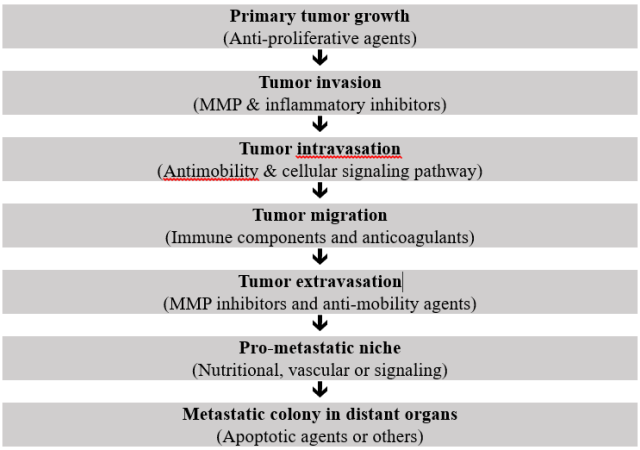

Figure 1 Proposed strategies targeting in different stages of invasive-metastatic cascade

Different types of tumor origins and metastatic sites

Generally, there are different subtypes of cancer in histologic origins, genetic status and metastatic organs. As a result, different types of anti-metastatic agents or drugs should be designed and manufactured. Their therapeutic mechanisms and clinical drug selection strategies should be promoted based on devoid of relevant pharmacological systems and architectures in the clinic. Theoretic breakthroughs in this area should be aimed.

Therapeutic modality in the clinic

General condition in clinical trials

Therapeutics to cancer metastasis has different strategies and modality that shows different targets and mechanisms. Expanding therapeutic modality study may boost drug development, combination and clinical trials in a long run. Herbal medicine and PM are especially popular for present cancer treatment. As a result, diagnostic, pathological and cancer hallmark study may boost anti-metastatic drug develop. Table 2 shows the landscape of different targets, modality and strategies.

Herbal medicine

Cancer treatment by herbal medicine is promising in the clinic because they treat disease in whole-bodies and multiple functionality as well as aim at long processes of disease management.[54–57] They are popular in India, China and other eastern countries. However, they are supported with different theories and medical knowledge among different countries and cultures. Global exchange and communications for medical knowledge and theories about herbal medicine may be useful and updated for prescribe his type of clinical trials and drug development.

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Table 2 Modern therapeutic modality for neoplasm metastases

Therapeutic modality types	Characters
Therapeutics of multi-disciplinary	Oncology Co-morbidity Teams of different trades Pathology-drug relation
Structural and molecular information	Chemo-physics relation Miniature systems for vast chemical comparison Diagnosis-based drug selection
Drug combination strategy	Multi-steps of neoplasm metastasis Intermediate states of tumor Drug selection and combination Heterogeneity of tumor cells in one nodule
Personalized medicine	Drug sensitivity testing Pharmacogenetics/ pharmacogenomics Tumor biomarkers Tumor bioinformatics Cost-effective consideration

Molecular targets, mechanisms and therapeutic paradigms

Different drug targets and mechanisms are fundamental issues for anticancer drug evaluation, study and development, including anti-metastatic drugs.[58–65] They are cell-signal inhibitors, AMF, HGF/c-Met, TGF-β inhibitors, β-catenin inhibitors,[64] cell movement inhibitors and many others. Most of these disease diagnosis of metastatic-related targets and inhibitors have not been licensed as anti-metastatic drugs but have a great potential for future clinical treatment. The more these targets and mechanisms have been studied, the more usefulness of clinical drugs and therapies could be expected. For these vast ranges of cancer-related molecular targeting, pathogenesis and pharmacology study may boost drug development.

Personalized medicine

Cancer is a different disease with a feature of unlimited cell growth and long survivals. Different tumors need different drugs and therapeutics. To implement high-quality anti-metastatic treatment in the clinic, personalized cancer therapy (PCT) will be served in future.[66–69] Previously, we gave a full picture of cancer personalized medicine in the earliest.[66] This type of therapeutic progressed greatly. They are mutual beneficial for drug development, clinics and knowledge.

Now, they are promising for therapeutic promotion and drug selection in the clinic. There are different types of PCT in experimental studies and clinical applications.[67–69] They are cancer biomarkers,[70] pharmacogenomics,[71] individual anti-metastatic treatment[72] and drug sensitivity testing.[73–77] By understanding the properties of different disciplines, we can have good drug selection in the clinic and save life of million in the future.Currently, drug sensitivity testing is mostly related with anti-metastatic therapies and drug selection. Their major techniques have been systematically progressed within the past decade.[73–75] These technique progress will continue to grow in the future.

Drug combination promotion

Anticancer drug combination has beneficial outcomes and efficacy promotion in many clinical circumstances. However, there is no guiding rule for drug combination in the clinic. In our early study, underlying principles, mechanisms or paradigms of drug combination optimism are useful avenue and play key roles for therapeutic updating in the future[78,79] -including the study of every possibility and new modality by updating therapeutic combine knowledge.

Future direction

Main scopes

Anti-metastatic treatment and drug development need great progresses. Several approaches are potential pathways for strategy promotion (Table 3).

Table 3 Roadmap for updating therapeutics

Methods	Utilizations
New drug target discovery	Antimetastatic drug developments
Drug administration or schedule analysis	Treatments with high efficiency
Mechanistic study	Novel drug discovery (new categories)
Diagnostic studies	Drug selection in the clinic
Metastatic cascade study	Properly use antimetastatic therapy
New active antimetastatic drugs	Metastatic nodule treatment

i. Spontaneous metastasis (subcutaneous or orthopedic inoculation)

ii. Artificial metastatic models (tail vein or intra-spinal)

iii. Circulating tumor cells (isolation and biomarkers)

iv. Mathematical modality (equation, algorithms and statistics)

Animal tumor models

Currently, animal metastatic models remain to be updated. A lot of good metastatic models must be created and further utilized in drug evaluation and development, especially in animal models.[80–82] For these metastatic models, in vivo evaluation has a high-demand and advantageous. They are more relevant than those in vitro tumor models. More recently, animal models are not limited in pulmonary metastasis. Brain, bone, liver or other organ metastases are also accounted and evaluation for new agents.

Pharmaceutical updating

Drug treatment need certain level of drug concentration in pathogens or tissues—including metastatic foci at remote sites. Drug carriers can guide effective drugs into tumor tissues or pre-metastatic niche. At present anticancer nano-drugs approximately consist of same number of normal anticancer drugs, licensed in Food and Drug Administration, United States (FDA, US). Further drug evaluative and development progress will be seen in the future.[4]

Global participations

Anticancer drug development is entering into a bottleneck stage from a great expanding of tumor models and sophisticate

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technology.[12–14,83–86] Due to these cutting-edge technology, the research and evaluative fund is boosting than ever before. Therefore, repeat work should be avoided. As a result, global participation is indispensable.[85] From global expanding of knowledge exchanges and co-funding, many drug related areas and study will achieve breakthroughs. Greater parts of financial feedbacks and industrial profit can be distributed to different labs and institutions in different countries. If this is workable, drug develop will be promoted quickly.

Conclusion

Cancer metastasis is the main cause of human mortality. Patho-therapeutic relationship should be promoted and accumulated in new medical knowledge. If we adhere on metastatic therapeutic study, we might save life of millions every year. In this regard, we should be optimized research outcomes from systematically diagnostic and therapeutic approaches.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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