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Drug Resistance Mechanisms in Breast Cancer Liver Metastases: Challenges and Opportunities

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Abstract

The liver is one of the most frequent locations for distant metastases in breast cancer patients, and breast cancer is the primary reason for cancer-related deaths in women globally. There are few therapeutic choices available for patients with breast cancer liver metastases, and drug resistance is common, which results in a bad prognosis and a short survival. Immunotherapy has a very poor therapeutic effect on liver metastases, and they are also resistant to chemotherapy and targeted therapies. Consequently, it is essential to comprehend the mechanisms of medication resistance in patients with breast cancer liver metastases in order to create and optimise treatment methods as well as to investigate alternative therapeutic options. We outline current developments in the study of drug resistance mechanisms in breast cancer liver metastases in this review and talk about the therapeutic potential of these mechanisms to enhance patient prognoses and outcomes.

Keywords: Breast cancer • Liver metastases; Drug resistance • Tumor microenvironment• Metabolic microenvironment

Introduction

Liver metastases are among the most frequent solid metastases from breast cancer, and they typically occur in the bones, lungs, liver, and brain. The liver is one of the most common sites of metastatic recurrence when compared to other common sites of metastasis. Breast Cancer Liver Metastasis (BCLM) occurs clinically in 40%–50% of cases, and the mortality rate is 50%–62%. The average Overall Survival (OS) for BCLM patients who are getting treatment is 31.0 months. The method of creating BCLM is intricate. The "seed and soil" idea, put forth by Stephen Paget in 1889 to describe the procedure, is still the widely accepted theory. Paget likened cancerous cells to "seeds" and the place where they spread to "soil." He asserted that the compatibility of the seeds (disseminated tumour cells) with the soil is a prerequisite for distant tumour metastasis (metastatic organs). The distinctive tissue features of the liver and the circulatory system play a significant role in the regulation of BCLM. In addition, chemokines, cell adhesion molecules, and inflammatory substances are also implicated. The prognosis is poor and medication resistance is frequent in BCLM patients. There are two types of drug resistance: primary and acquired. Primary resistance, as the name suggests, describes tumours that resist the first round of therapy. Acquired medication resistance emerges after protracted therapy for malignancies that at first respond to therapy. Tumor burden and growth kinetics, tumour heterogeneity, the physical barriers of the cell membrane, the immune system and milieu, insurmountable cancer drivers, and the effect of medication pressure are among the "key factors" of tumour resistance. The formulation and improvement of treatment plans will be facilitated by a deeper comprehension of the mechanisms of medication resistance that exist in BCLM patients. This review examines the therapeutic potential of current developments in the investigation of medication resistance mechanisms in BCLM in order to enhance patient prognosis. Breast cancer cells can enter the bloodstream via penetrating the endothelium of tumour arteries. Breast cancer cells can survive in the bloodstream. Marginality: Circulating breast cancer cells bind to sinusoidal endothelial cells via certain adhesion molecules to arrest at the liver location. Breast cancer cells extravasate through sinusoidal endothelial cells, enter the liver, and then multiply there. Breast cancer cells persist in the hepatic milieu and create micrometastatic foci. Kupffer cells, hepatic sinusoidal endothelial cells, Hepatic Stellate Cells (HSCs), pit cells, lymphocytes (such as natural killer T cells), gamma-delta T cells, dendritic cells, etc. are among the immunoreactive cells abundant in the liver as an immune organ. Moreover, the liver creates immune-related molecules that are important for systemic inflammation and immunity, such as C-reactive protein and soluble pattern-recognition receptors. Due to its embryonic origin as a hematopoietic organ, the flow of portal blood from the gastrointestinal tract and spleen into the liver, as well as mucosal immunity from the biliary system through the excretion of metabolites, the liver has a unique immunotolerant microenvironment despite being rich in immune cells. Hepatic sinusoidal endothelial cells lack a basement membrane, in contrast to normal capillary endothelial cells. Since lymphocytes are in close contact with hepatocytes, this increases the exchange of chemicals between hepatocytes and blood. because bacterial components and food antigens regularly move through the portal vein from the gastrointestinal tract into the liver. A distinct immunotolerant microenvironment is created when the liver maintains a degree of tolerance that balances the clearance of bacterial pathogens and prevents excessive inflammation brought on by the nonpathogenic intestinal environment. According to a mouse study, the liver's distinct immunotolerant microenvironment plays a significant role in liver tumours' resistance to anti-programmed cell death protein 1 (PD-L1) antibody therapy, regardless of the tumor's kind or origin. 29 Moreover, Yu et al. discovered that the liver metastases drain activated CD8+ T lymphocytes from the systemic circulation utilising various mice models. Activated antigen-specific Fas+CD8+ T lymphocytes die in the liver through contact with FasL+CD11b+F4/80+ monocyte-derived macrophages.Therefore, liver metastases induce a systemic immunological desert in preclinical animals. 30 It has been shown that liver metastases can induce acquired immunotherapy resistance by

exploiting host peripheral tolerance mechanisms through CD8+ T cell deletion. 30 By increasing T cell immunoglobulin and mucin domain 3 (TIM3) expression in natural killer cells through degradation of miR-449c-5p, exospheric plant Homeodomain and Ring Finger Domain 1 (HRF1), which is derived from Hepatocellular Carcinoma (HCC), promotes immune escape and PD1 resistance to PD-1) immunotherapy. Furthermore, immunotherapy together with liver-directed radiation therapy can strengthen systemic antitumor immunity. It is interesting to note that despite the unfavourable outcomes of immunotherapy for liver metastases, treatment with targeted PD-1 monoclonal antibody has showed some promise in treating primary HCC. The US Food and Drug Administration authorised tecentriq, which targets PD-L1, in conjunction with avastin for clinical usage in May 2020. As second-line therapies for HCC, cabozantinib, keytruda, nivolumab, and nivolumab plus ipilimumab are now accepted. 33 The combination of interferon and anti-PD-1-based immunotherapies has also been shown by Hu et al. to have promising anticancer effects in HCC patients. Also, they have proposed a mechanism for the synergistic effect of interferon and anti-PD-1 antibodies in HCC; they contend that the combination therapy changes the tumor-immune milieu by encouraging CD27+CD8 + T cell infiltration, which then results in HCC tumour regression. Moreover, combined immunotherapy has demonstrated promise in a range of tumour types. PD-1 antibody and cytotoxic T lymphocyte-associated antigen-4 antibody combination therapy is now licenced for the treatment of some malignancies. Nivolumab and ipilimumab, for instance, have been authorised for the treatment of melanoma, non-small cell lung cancer, HCC, and renal cell carcinoma. Combination immunotherapy may also provide an innovative new approach to the management of BCLM, and as such, its involvement in BCLM merits further investigation. It is important to note that immune combination therapy patients may face greater rates of grade toxicity, and some immune combination therapy clinical trials have been stopped as a result. While considering immunological combination therapy for BCLM, the possibility for severe immune-related toxicity must be taken into mind due to the unique role the liver plays in drug metabolism. Induced by local tissue hypoxia and acidosis, Vascular Endothelial Growth Factor (VEGF), the most well-established biological modulator of tumour angiogenesis with concurrent immunosuppressive effects, stimulates the formation of flawed and leaky tumour vasculature. In addition to its indirect effects on anti-tumor immunity through its influence on blood vessels by preventing immune effector cell penetration of tumours, VEGF also has direct local and systemic immunosuppressive effects. The immune suppressive effects of VEGF, which are linked to increased infiltration of regulatory cells, myeloid-derived suppressor cells, and M2 type Tumor-Associated Macrophage (TAM) into tumours, are reversed by anti-VEGF therapy. Also, it has been discovered that PD-1 targeting combined with VEGF suppression is an efficient way to treat liver metastases. In a mouse model of colorectal cancer liver metastasis, researchers discovered that inhibiting VEGF lowered the number of PD-L1 + and TIM3+ infiltrating T cells. Additionally, when PD-L1 alone was suppressed, mice subcutaneously injected with colon cancer cells did not exhibit a discernible antitumor effect. Yet when the medication was paired with VEGF inhibitors, they did demonstrate a significant decrease in tumour burdenThis shows that the combination of anti-angiogenic medicines and immunomodulators of inhibitory checkpoints may be advantageous for liver cancers that produce VEGF-A. MicroRNA (miRNA)-934 is an example of a non-coding ribonucleic acid that induces TAM differentiation to the M2 phenotype, facilitating tumour development and metastasis as well as mediating treatment resistance. GRP78, a member of a family of highly conserved heat shock proteins, regulates glucose. Important stress-response functions include its involvement in cellular metabolism, hypoglycemia, hypoxia, acidosis, viral infection, and DNA damage repair. It also plays a role in the Unfolded Protein Response (UPR) and endoplasmic reticulum stress responses. Also, it has been shown that the in vitro overexpression of Cell Surface (CS) GRP78 improves the colonisation and proliferation of breast cancer tumour cells in the liver as well as their invasiveness. Moreover, GRP78 expression is linked to treatment resistance and cancer cell invasion. Endoplasmic reticulum stress pathways cause a signalling network known as the UPR to become active in cancer cells. GRP78 controls UPR, making tumours more resistant to chemotherapy. Breast cancer tumour development and reduced insulin-like growth factor binding protein 3 entry are both facilitated by GRP78. Tseng et al. discovered that signal transducer and activator of transcription could be activated by the C-terminal domain of CS-GRP78 to cause tamoxifen resistance in breast cancer (STAT3).

According to the aforementioned data, GRP78 might be to blame for the emergence of drug resistance in BCLM. Although the function of immune cells present in the tumour microenvironment is generally thought to be regulated by GRP78, the precise method by which this occurs is yet unknown.

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