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Treatment of Metastatic Cancer: Focus on Brain, Lung, Bone, Liver, Malignant Effusions, and Ascites

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ABSTRACT

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Metastatic cancer is a formidable clinical issue, involving malignant cells that travel from a primary tumor site to a distant organ. This manuscript summarizes the current treatment options for metastatic disease burdening the brain, lungs, bones, liver, malignant effusions, and ascites. Each possible metastatic site involves its own clinical considerations of tumor biology, symptom burden, and the patient's performance status. Metastatic diseases involving the brain may require corticosteroids, resection, stereotactic radiosurgery or whole brain radiation therapy, and/or systemic therapies. Metastatic disease of the lung and liver often involves a multi-modality approach that incorporates systemic chemotherapy, possibly systemic targeted agents, localized ablative therapies, and possibly palliative surgical therapy in an oligometastatic setting. Bone metastases often include a combination of analgesics, bisphosphonates or RANK ligand inhibitors, radiation, and sometimes orthopedic stabilization and reconstruction. Malignant pleural effusions and ascites are common in patients with advanced diseases and a number of procedures can be utilized including drainage procedures, intrapleural or intraperitoneal therapies and systemic therapies. Individualized, multidisciplinary care has been shown to improve symptom management and quality of life in palliative settings and may lead to a longer survival in specific circumstances.

KEYWORDS:

Cancer, treatment, Chemotherapy, immunocompromised , Pallative Anti tumor,immunotherapy

INTRODUCTION

Metastatic cancer, which occurs when cancer cells spread from the primary tumor location to distant organs, continues to be one of the most common causes of cancer-related morbidity and mortality. The prognosis of metastatic disease can frequently be associated with a poor prognosis, however, the treatment landscape is changing due to the development

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Estimated number of new cases in 2020. worldwide, both sexes, all ages (left), and estimated number of deaths in 2020. worldwide, both sexes, all ages (right). (Data source: GLOBCAN 2020, Graph production: Global Cancer Observatory

1. Brain Metastases

Brain metastasis is one of the most common places for metastatic disease, and it is common with lung cancer, breast cancer, melanoma, and kidney cancer. The blood-brain barrier (BBB) presents one of the biggest obstacles for treatment with respect to systemic therapies.

Surgically Resectable Brain Metastases & Radiation TherapyIf brain metastases are accessible resection is the standard of care, generally, when the brain metastasis is a single, well-circumscribed tumor, and surgery is not generally an option for treatment when patients have multiple metastases. When multiple metastases are present, stereotactic radiosurgery (SRS) with Gamma Knife|CyberKnife is the standard of care for the management of oligometastatic brain disease. SRS is an effective non-invasive treatment option that can accurately deliver radiation while limiting damage to surrounding normal tissue.

Systemic Therapies and Immunotherapy In recent years, immunotherapeutic advances have been reported in the management of brain metastases. Systemic use of immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab) have been effective in the management of brain metastases from melanoma and NSCLC (non-small cell lung cancer) metastasis (Ni et al., 2021).

Immune checkpoint inhibitors such as these target PD-1 or PDL-1 to enhance T-cell-mediated immune response to eradicate tumor cells. Targeted therapies in systemic treatment for brain metastasis have also been seen to be efficacious, including EGFR inhibitors (osimertinib) for EGFR-mutated NSCLC or BRAF inhibitors (dafrafenib) in melanoma with BRAF mutations (Buchanan et al., 2020). Unfortunately, the continued use of multiple systemic treatments can also requires careful management of safety and effectiveness at the level of the blood-brain barrier, and is also limited in application.

2. Lung Metastasis

Lung metastasis is not uncommon due to the anatomical and physical attributes these organs present. The metastases typically arise from breast, kidney, colon, and melanoma etiology. Lung metastases are treated based on the primary cancer, total number of metastases, and the patient's general health.

Surgical Resection

Surgical resection is often pursued when there are limited numbers and within a resectable site.

Surgical excision would have the possibility for long-term survival, when adjuvant systemic therapies are also used. Patients, however, are often limited to one, or in a very few number of metastases.

Systemic Chemotherapy and Targeted Therapy

Systemic chemotherapy remains the standard treatment for patients with multiple lung metastases. Platinum-based regimens, especially when employed with other agents (e.g., gemcitabine, pemetrexed) remain at the very least a standard of care for numerous metastatic cancers. Targeted therapies (i.e., EGFR and ALK inhibitors) and immune check-point inhibitors are changing treatment paradigms and survival outcomes for patients with NSCLC (Gandhi et al., 2018).

Radiation Therapy

Stereotactic body radiation therapy (SBRT) is becoming more frequently used for localized lung metastases, especially when surgical resection is not an option. Stereotactic body radiation therapy (SBRT) is a technique that allows for the delivery of a high dose of radiation to a specific area, allowing for more focused treatment with less side effects.

3. Bone Metastasis

The bone is a common site of metastasis, particularly with breast, prostate, and lung disease. Bone metastases can lead to significant morbidity, including pain, fractures, spinal cord compression, and hypercalcemia.

Palliative Radiation Therapy

Palliative radiation therapy is often used for treating pain from bone metastasis. SBRT is particularly effective for localized bone lesions and can provide long-lasting pain relief.

Bone-Targeted Therapies

For patients with extensive bone metastases, bisphosphonates (e.g. zoledronic acid) or denosumab (a monoclonal antibody targeting RANKL) are frequently used to lower the risk of skeletal-related events (Sammarco et al., 2020). These agents inhibit osteoclast-mediated bone resorption and are able to maintain bone integrity.

Systemic Therapeutics

Systemic chemotherapy can be combined with targeted therapies (e.g., HER2-positive breast cancer) to try to control tumor progression. For bone metastases in prostate cancer, there are therapies including androgen deprivation therapy (ADT) and

chemotherapy (e.g., docetaxel) to help control the disease.

4. Liver Metastasis

The liver is a common site of metastasis from multiple primary tumors, mainly colorectal cancer, pancreatic cancer, and breast cancer. The prognosis for patients with liver metastasis is frequently poor; however, surgical and local therapies can be useful.

Surgical Resection and Liver Transplantation

In selective patients with isolated liver metastases, surgical resection is often a consideration, especially in colorectal cancer, where 5-year overall survival can be up to 40% in patients who have been surgically resected (Adam et al., 2012). In rare circumstances, liver transplantation may be considered for certain tumor types or characteristics.

Ablation Procedures

Microwave ablation and radiofrequency ablation (RFA) are methods that are minimally invasive for patients with small isolated liver metastases. These treatments involve destroying tumor tissue by means of heat and can be done either laparoscopically or percutaneously.

Chemotherapy and Targeted Therapy

Systemic chemotherapy using regimens such as FOLFOX (oxaliplatin, leucovorin, and fluorouracil) and FOLFIRI (irinotecan, leucovorin, and fluorouracil) is the standard of care in the treatment of liver metastasis and is of particular relevance in the management of colorectal cancer. To target tumor vasculature and growth, options such as bevacizumab (an anti-VEGF antibody) or EGFR inhibitors (e.g., cetuximab) may augment the regimens (Kohn et al, 2018).

5. Ascites and Malignant Effusions

Malignant ascites and pleural effusions are frequently seen in advanced malignancies, particularly in lung, breast, ovarian, and gastrointestinal tumors. These complications are frequently associated with poor prognosis and are primarily palliative in order to optimize quality of life.

Management of pleural effusions

Thoracentesis is performed to drain pleural effusions, giving symptomatic relief from symptoms such as dyspnea. Indwelling pleural catheters (e.g., PleurX) are employed for effusions that repeatedly reoccur, as patients can manage drainage at home. In patients with established and continuous effusions,

pleurodesis (a chemical approach inducing pleural adhesion to block fluid reaccumulation) can be considered.

Management of ascites Paracentesis removes ascitic fluid to provide symptomatic relief. In patients with recurrent ascites, consideration may be given to a peritoneovenous shunt or TIPS (transjugular intrahepatic portosystemic shunt). Administering systemic chemotherapy or targeted therapies to treat



Age at prevalence

<50 years 50-64 years 65-84 years 85+ years</p>

the underlying malignancy will assist in controlling fluid reaccumulation.

Immunotherapy and targeted approaches

New and emerging therapies targeting the tumor microenvironment such as immune checkpoint inhibitors and anti-angiogenic agents show promise in reducing fluid production in malignant effusions and ascites (Cavalieri et al., 2020).

Years since diagnosis

<5 years 5- <10 years 10 - <15 years 15 - <20 years 20+ years</p>

Percent

Prevalence by Cancer Type, Years Since Diagnosis, and Age at Prevalence as of January 1, 2022, United States. Estimates do not include in situ carcinoma of any site except urinary bladder and do not include basal cell or squamous cell skin cancers. ^aCancer prevalence for survivors of prostate cancer <50 years of age is <1%.

CONCLUSION

Metastatic cancer is complex and treatment options will depend on the site of metastasis and the molecular characteristics of the primary tumor. Traditional therapy modalities still continue to be key players in the treatment of metastatic cancer in the form of surgery, chemotherapy, and radiation, while newer options and modalities such as

targeted therapy, immuno-oncology, and other refinements of image-guided therapies provide a more specific, less toxic option for patients. As we learn more in research, the treatment of metastatic cancer has the potential to be more individualized, ultimately increasing survival and better quality of life for patients.



Immunological nanomaterials to combat cancer metastasis

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