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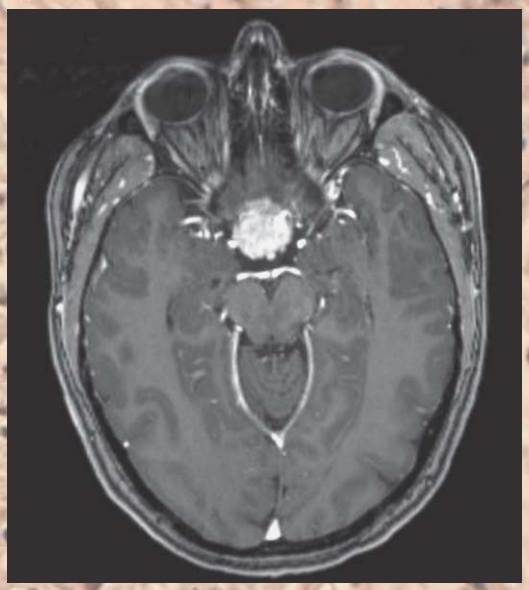

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Brain Metastases: A Meeting Report from the Annual Meeting of the American Society of Clinical Oncology 2013*

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Brain metastases (BM) are the most common intracranial malignancy in adults with an incidence 10 times higher than in primary malignant brain tumours. Besides the high and rising incidence, brain metastases have an impaired and poor prognosis with survival times of only several weeks to a few months. However, treatment options, especially in terms of systemic therapy approaches, are very limited. The number of brain metastases (>/< 3 metastases) as well as their sizes (>/< 3 cm diameter) are groundbreaking for further treatment approaches. Patients with ≥ 3 brain metastases are candidates for an either surgical (brain metastases > 3 cm) or radiosurgical (brain metastases < 3 cm) treatment approach with facultati-ve adjuvant whole-brain radiation therapy. Patients with > 3 brain metastases are usually treated with whole-brain radiation. Therefore, brain metastases pose a great clinical need for improved treatments that is, however, not reflected by the number of studies investigating brain metastases.

The Annual Meeting of the American Society of Clinical Oncology (ASCO) is one of the most prominent scientific conferences. The plenary session is followed by > 25,000 participants and the results presented have high impact on clinical practice. In the following, we give a short overview concerning the presented articles on BM at the ASCO 2013 meeting.

Prognostic Assessment in Patients with Brain Metastases

Several prognostic scores for estimation of survival time upon first diagnosis of brain metastases exist. The diagnostic, specifically graded prognostic assessment takes clinically prognostic factors into account as well as the histology of the primary tumour, resulting in a specific prognostic score for each primary tumour [1]. The graded prognostic assessment for breast cancer includes age, receptor (eg, oestrogen receptor, HER2 receptor) expression, and Karnofsky performance status and was once more validated for a cohort of patients treated at a tertiary care centre [2]. Another study on breast cancer brain metastases tried to identify clinically prognostic factors for long-term survival over 36 months. However, none of the common clinical factors showed a significant association with long-term survival [3]. In a further retrospective cohort of breast cancer patients who underwent craniotomy for brain metastases, only age showed prognostic impact on overall survival [4].

Graded prognostic assessment was validated in a real-life cohort of patients with non-small lung cancer brain metastases [5]. Presence of EGFR mutation was identified as an independent prognostic factor upon diagnosis of non-small cell lung cancer brain metastases [6]. A population-based study investigated factors associated with the risk of brain metastases at first diagnosis of non-small lung cancer. A score including age > 60, non-squamous histology, size > 5 cm, grade II–IV, and lymph node involvement was postulated to stratify for patients with an increased risk for brain metastases [7].

As no specific prognostic score exists for renal cell carcinoma, the value of the graded prognostic assessment including the factors age, Karnofsky performance score, number of brain metastases, and status of extracranial disease was evaluated for renal cell carcinoma brain metastases. However, no significant correlation of the graded prognostic assessment score and overall survival was evident and a new prognostic assessment based on the factors time from diagnosis of primary tumour to brain metastasis, haemoglobin level, age, number of brain metastases, and status of extracranial disease was postulated [8]. Another study postulated the MSKCC (Memorial Sloan Kettering Cancer Center) risk group, histology (clear-celled vs other), and number of brain metastases as prognostic factors in a similar, independent cohort of patients with renal cell carcinoma brain metastases treated with various targeted therapies (anti-angiogenic, mTOR inhibitor) [9].

Graded prognostic assessment was validated for brain metastases from melanoma, indicating that the presence of liver metastases and haemorrhagic metastases adds additional prognostic value [10].

Rare Primary Entities of Brain Metastases

Lung cancer, breast cancer, and melanoma are the most common primary tumours of brain metastases and brain metastases are very rare in other primary tumours. However, some studies presented at ASCO 2013 focused on prognostic factors and development of brain metastases in rare primary entities [11–15].

Although colorectal cancer is a frequent cancer entity patients rarely develop brain metastases as most patients die due to

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systemic progression before the development of brain metastases. Data of a large retrospective study postulated an increased risk for brain metastases of colorectal cancer in patients with lung metastases and KRAS mutation [11].

Brain metastases of non-seminomatous germ cell tumours are rare. However, up to 15 % of patients might eventually develop brain metastases. Patients with elevated hCG levels > 500 IU/l, multiple (< 3) and large (< 2 cm) pulmonary metas-tases, and a poor IGCCCG prognosis score are at a higher risk of brain metastases and screening in this patient population was suggested to be feasible [12]. In addition, the possibility of long-term survival for patients with brain metastases of germ cell tumours irrespective of their time of occurrence (synchronous or metachronous to the first diagnosis of germ cell tumour) was postulated [13].

The incidence of brain metastases was evaluated in a rare series of 21 patients with primary cardiac sarcoma. 33 % developed brain metastases, although brain metastases are very rare in sarcoma patients – commonly, they occur only in about 8 % [14]. Similarly, the incidence of 1.8 % for brain metastases was reported for a retrospective cohort of patients with metastatic urothelial carcinoma, an entity that rarely metastasizes to the brain. Survival upon diagnosis of brain metastases was poor with a median of only 3 months [15].

Pathobiology of Brain Metastases

The understanding of the metastatic cascade and the molecular function involved is crucial to direct further development of treatment approaches [16].

Melanocytes and glial cells share their ectodermal origin, an instance that is commonly used to explain the high propensity of melanoma to metastasize to the brain. Herein, a high expression of neutral factors, namely the p75 neurotrophin receptor, was observed in cell lines of melanoma brain metastases, supporting the theory of neurotrophin receptor involvement in the brain metastatic cascade [17]. Another study on the pathobiology of melanoma brain metastases investigated alterations in DNA methylation patterns, which are recognized markers of metastasis initiation. Significant genome-wide hypomethylation and CpG island hypermethylation were observed [18].

An autopsy study focused on the invasion of brain metastases into the surrounding brain parenchyma. Herein, 3 different invasion patterns were postulated: (1) well-demarcated (clearly distinct border of brain metastases and brain parenchyma), (2) vascular co-option (growth along pre-existing vessels), and (3) diffuse infiltration (single-cell infiltration of the surrounding brain parenchyma) [19].

A preclinical mouse model study of melanoma brain metastases examined the potential role that the drug efflux transporters p-glycoprotein and breast cancer-resistant protein play in the treatment response of melanoma brain metastases harbouring the BRAF V600E mutation to the BRAF inhibitor vemurafenib, indicating that these might be involved in mechanisms of resistance [20].

The RAF-MEK-ERK and the PI3K-Akt pathways play a crucial role in the progression and metastatic spread of melanoma. A preclinical study therefore investigated the value of a new PI3K inhibitor. Herein, the PI3K inhibitor BKM120 produced a significant reduction of cell growth in the metastatic melanoma cell line and in a melanoma brain metastases mouse model [21].

Molecular features like the EGFR status in non-small cell cancer were postulated to influence the propensity of brain metastasis development. A multivariate model including EGFR mutation, young age, and lymph node involvement was shown to predict for patients at a higher risk for brain metastasis development [22].

Treatment of Brain Metastases

Patients with brain metastases have been systematically excluded from clinical trials in the past and clinical trials on the specific treatment of brain metastases are rare [23]. However, the inclusion of patients in clinical trials is the key approach in improving treatment strategies. Only few studies presented at the ASCO 2013 focused on treatment options in brain metastases and even less clinical trials including patients with brain metastases were presented.

Only one phase-III study including patients with brain metastases from non-small cell lung cancer was presented. Herein, the value of additional oral systemic therapy with topotecan in addition to whole-brain radiation therapy in patients with non-small cell brain metastases was evaluated. However, no significant impact of additional therapy with topotecan but significantly higher rates of adverse events were evident [24].

The combination of stereotactic radiosurgery followed by immunotherapy with the CTL4A antibody ipilimumab was shown to be active and safe in 2 independent small cohorts of patients with melanoma brain metastases [25, 26].

Systemic therapy with the BRAF mutation inhibitor vemurafenib was investigated in several, independent small cohorts of patients with melanoma brain metastases harbouring a BRAF mutation. A response rate of up to 50 % was observed, however, a discordance of the response in intra- and extracranial lesions was evident in some patients [27, 28]. The high impact of BRAF inhibitors in the treatment of patients with melanoma brain metastases was further emphasized by a retrospective evaluation, indicating that patients treated with a BRAF inhibitor experience median survival times of up to 23.2 months compared to 6.7 months in patients not treated with a BRAF inhibitor [29].

A response rate of up to 80 % with a very favourable toxicity profile was shown in a phase-II study of icotinib, a new epidermal growth factor receptor tyrosine kinase inhibitor, in combination with concomitant whole-brain radiation therapy for brain metastases of non-small cell lung cancer [30].

Vorinostat showed promising radiosensitizing effects in preclinical models. Hence, the safety of vorinostat as a radio-

sensitizer in brain metastasis patients undergoing whole-brain radiation was shown [31].

The value of the epidermal growth factor receptor tyrosine kinase inhibitors sunitinib and sorafenib was further evaluated in a very small, single-centre cohort with renal cell cancer brain metastases. Herein, an overall response rate of 27 % was observed [32].

Two phase-II studies investigated bevacizumab-based systemic therapy in patients with brain metastases. (1) A non-comparative study showed promising results and safety for the combination of bevacizumab with carboplatin and paclitaxel as first-line treatment or erlotinib and bevacizumab as second-line treatment in patients with asymptomatic non-small cell lung cancer brain metastases [33]. This result was further supported by (2) a small study postulating an intracranial response rate of 78 % and an extracranial response rate of 40 % for bevacizumab-based treatment [34].

A phase-II trial of carboplatin and bevacizumab in patients with breast cancer brain metastases showed promising results with an overall response rate of 63 % and a progression-free survival of 5.7 months. Based on this data, a phase-III trial is being considered by the authors [35].

While the studies mentioned so far concentrated on the treatment of established brain metastases, 2 independent studies focused on the potential of bevacizumab-based treatment to prevent the occurrence of brain metastases in patients with advanced non-small cell lung cancer. A statistically significant reduction of the propensity of brain metastases was observed in patients receiving bevacizumab-based therapy compared to patients treated with chemotherapy only in both retrospective series [36, 37].

Similarly, a preventive value of erlotinib therapy in terms of brain metastasis development was postulated as patients receiving erlotinib-based therapy had less brain metastases and developed them later during the course of their disease than patients treated with chemotherapy only [38].

The penetration at active concentrations and the passage through the blood-tumour/brain barrier is one of the major obstacles in the systemic treatment of brain metastases. The value of the blood-tumour/brain barrier in brain metastases is currently under discussion. Therefore, somewhat surprisingly a study investigating the drug concentration of capecitabine and lapatinib in resected brain metastases from breast cancer postulated concentrations of 21–1422 % of the serum concentration, underscoring the already known clinical activity of these drugs in the treatment of breast cancer brain metastases [39].

Conclusion

In conclusion, the further inclusion of patients with brain metastases in randomised clinical trials and further basic research on the brain metastatic cascade are urgently warranted to identify drugable targets.

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