Brain Metastases: Finally a Light at the End of this Long Dark Tunnel

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This is to acknowledge that Dr. Maher has disclosed that she does have financial interests or other relationships with commercial concerns related indirectly to this program (Agios Pharmaceuticals, Site PI on Phase I clinical trial of IDH1 inhibitor and co-PI of Sponsored Research Agreement with Peloton Pharmaceuticals). Dr. Maher will be discussing off label uses of molecular targeted therapies in her presentation.

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Interests:
Malignant glioma
Metastatic brain tumors
Metabolism and imaging of brain tumors
Mouse modeling of gliomas and brain metastases

Purpose and Overview:
The goal of this presentation is to review the state of the field of brain metastases including diagnosis and clinical management. In addition, barriers to progress will be discussed and what scientific and translational questions need to be addressed in order to make progress in developing effective therapies.

Objectives:
1. To understand the role of surgery, radiation therapy, and chemotherapy in the management of patients with brain metastasis.
2. To identify the tumors for which molecular targeted therapies may have a role in management and describe the role that clinicians can play in driving progress through inclusive clinical trials.
3. To understand the need for robust preclinical models of the brain metastasis tumor subtypes and the role that these models can play in advancing drug discovery and preclinical testing.

Overview

A major clinical problem

Brain metastases from solid tumors affect approximately 200,000 patients per year in the US. Untreated, the median survival is 2 to 3 months and with aggressive multimodality treatment, survival is extended marginally to an average to 4-12 months[1]. Radiation, either whole brain or stereotactic radiosurgery, is the mainstay of treatment, with surgery reserved for patients with large symptomatic metastases and cytotoxic chemotherapy rarely used because of lack of benefit. During the long history of drug development in cancer, clinical trials have excluded patients with brain metastases because of their short survival time and the lack of CNS penetration of most drugs. The net result is improved overall survival in many cancers but with an alarming increase in the frequency of brain metastasis development[2]. The failure of effective first line therapies to penetrate the blood brain barrier has effectively created a sanctuary site in the brain for metastatic cells. There are many unanswered questions about the biology of these cells, including the timing of metastasis relative to the primary disease and recurrence, mechanisms of brain homing, dormancy, and molecular drivers of growth in the brain. Tumors that rarely metastasized to the brain, for example thyroid cancer, are becoming more commonplace. Furthermore, patients who have well controlled systemic disease are developing brain metastases and dying from neurologic progression over a few short months, most notably young women with HER2 positive breast cancer treated with the monoclonal antibody, trastuzumab (Genentech) [3,4].

A Need for Centralized Clinical and Research Focus:

Progress in the treatment of brain metastases has been hampered by a lack of focus on the clinical problem over many years. The staggering impact of these short survival times is reflected in the total numbers. Over the past 25 years, approximately 4,250,000 cancer patients have died with brain metastases[2]. To date, the primary oncologist cares for patients with brain metastases obtaining short-term input from the radiation oncologist and neurosurgeons. Thus, in most academic centers there is no central clinic that sees these patients and manages the brain disease. This tends to diminish the magnitude of the growing problem and significance of the number of cases. The incidence of brain metastasis is 10 times higher than the number of primary brain tumors managed by neuro-oncology, with number approaching those seen in lung cancer,~225,000 cases, prostate cancer, ~230,000 cases, and breast cancer, ~230,000

cases. More alarming are the statistics for survival, where death from brain metastases far exceeds death from prostate and breast cancer, as well as many other cancer subtypes combined. It is impossible to overstate the urgency of the problem and the importance of a centralized focus on the biology and development of new therapies.

Lump or Split? Not simply an academic exercise.

Non-small cell lung cancer and breast cancer account for 65-75% of the brain metastases cases, reflecting the relative incidence of these two cancers in the general population among cancer subtypes that metastasize to the brain[2]. Melanoma and renal cell account for 5-10% and 5% of cases respectively, numbers disproportionate to their incidence among primary cancers, reflecting instead a high predilection for metastasis to the brain[5]. Nearly 27% of patients with metastatic melanoma have brain metastases and autopsy studies suggest that this number is closer to 75% by the time of death[6]. From an absolute risk perspective, advanced melanoma has a several fold greater likelihood of spreading to the brain compared to other malignancies, and the uniqueness of this predilection may lie in trophic mechanisms that are poorly studied and understood. Yet, despite the widely differing molecular signature profiles and differences in susceptibility to radiation and chemotherapy among the brain metastasis subtypes, they are most often "lumped" together as a single entity reflecting their common clinical presentation late in disease, progressive neurological impairment and short survival. While "lumping" the clinical subtypes grossly oversimplifies a complex problem that has significant patient and tumor heterogeneity, the common phenotypic presentation and endpoints suggest that common mechanisms underlying tropism, adaptation to the brain, and treatment resistance may exist and prove amenable to common therapies. “Splitting”, however, can identify subsets of patients who may respond to a specific agent. This is most notable for EGFR-mutated non-small cell lung cancer, BRAF-mutated melanoma and, HER2+ breast cancer, for which case reports and small studies describe responses in brain metastases (see below). These data represent the ‘light at the end of the tunnel’, in that they provide for the first time in a long history of failed therapies to show that identifying a drug that hits a driver pathway could be effective therapy. At the core is a fundamental question of what is the relative biological importance of the underlying cell of origin and/or molecular drivers versus growth of the tumor cell in the microenvironment of the brain. This classic “seed vs soil” question in brain metastasis has not yet been addressed scientifically but having some tumors able to respond

specifically to molecularly targeted therapies is a major conceptual advance. In addition, from a clinical perspective, the stage has been set for different protocols of screening patients for brain metastases during their treatment course (based on risk-group identification) as well as differences in recommended therapies and "prophylactic" strategies, which could potentially either impede the metastatic potential of the primary tumor or eliminate intracranial microscopic disease before it becomes clinically manifest.

Basic Science Questions: At a more basic level, the clear differences in metastatic potential raise the question as to whether some tumors are "hardwired" to metastasize to the brain. Does a molecular signature exist that either induces 'homing' to the brain or provides the necessary genetic alterations for the cell to interact at a microenvironmental level to grow in the brain? If such a genetic program exits, is it common among the various primary tumors? There has been a treasure trove of molecular data published from The Cancer Genome Atlas Project (TCGA) over the past several years. Essentially all the tumors studied have been primary tumors and have provided new insights into the molecular underpinnings of the various cancer subtypes. Coupled with clinical details about histology, response to initial treatment, timing and sites of metastasis, and survival time, hypotheses are being generated about the metastatic potential of the primary tumors and the molecular underpinnings of the cells that ultimately seed the brain. It is unfortunate that the molecular characterization of brain metastases was not undertaken as part of the TCGA project because that would have provided an opportunity to delve more deeply into questions about similarities and differences among the cancer subtypes and subgroups that spread to the brain. A comprehensive review of the biology of brain metastasis can be found in Nature Reviews/Clinical Oncology, April 2014 by Owonikoko and colleagues [7].

Current Treatment: Development of Practice Guidelines

Surgical Resection

Guidelines for the surgical management of brain metastases were developed and published in 2009 by the American Association of Neurological Surgeons [8,9]. Resection of a brain metastasis is indicated in a limited number of clinical scenarios. First, biopsy or complete resection may be performed for diagnosis although histologic confirmation is often not needed in the setting of metastatic disease. In the situation of delayed development of a single intracerebral lesion, several years after the primary cancer is

diagnosed, the false-positive imaging rate is low at approximately 11%. Second, large (>3 cm) or symptomatic masses are removed to palliate symptoms. Although resection of more than 1 lesion (generally 2 or 3) has also been advocated by some, no convincing data exist as to the value of such an approach. Surgery alone is inadequate treatment and thus many studies have been conducted to assess the role of whole brain radiation with or without radiosurgery.

Radiation therapy: Whole brain radiation and Stereotactic Radiosurgery

Whole brain radiation, in which the whole brain is treated with a uniform dose of external beam radiation, has been a standard therapy for many years. It is used to reverse acute neurological deficits and has been shown to prolong survival by 2 – 7 months [10]. Randomized trials have been done by The Radiation Therapy Oncology Group (RTOG) to determine dose, toxicity, and efficacy of radiation. Prognostic classes have been developed based on age, extent of systemic disease, and overall functioning (recursive partitioning analysis (RPA)) to guide treatment. High dose, focused radiation (radiosurgery) has also been used extensively to treat brain metastases. The maximum target volume is 3-4 cm and multiple metastases (usually up to 3) can be treated at the same time. Radiosurgery has a favorable toxicity profile, provides good local control in the brain while sparing normal brain. Randomized trials have demonstrated that enhancing intracranial control by radiosurgery followed by whole brain radiotherapy results in survival prolongation and improved functionality compared to whole brain radiotherapy alone in patients with single brain metastases. Although radiosurgery to more than 1 lesion (generally 2 or 3) has also been advocated by some, the data used to support this recommendation reflects subset analyses. Whole brain radiotherapy following surgery or radiosurgery unquestionably diminishes the intracranial failure rate. However, in all likelihood, it has limited to no effect on overall survival, at least in patients with multiple brain metastases, who are also more likely to harbor uncontrolled systemic disease. This may change as the number of patients who have brain metastases in the setting of well controlled disease increases. Whether surgery or radiosurgery requires additional whole brain radiation for overall control in the brain remains unclear. For a single (or fewer than 4) metastasis, the addition of whole brain radiation to surgery or radiosurgery has been shown to decrease recurrence in the brain from 70% to 18%, decrease local recurrence from 37% to 14%, and decrease neurological death from 44%

to 14%, although without an increase overall survival [11-13], with the caveat that these studies were never powered to detect a survival difference.

The American Society of Radiation Oncology convened a task group of experts in neurosurgery, radiation therapy and stereotactic radiosurgery to develop recommendations for management of brain metastasis based on extensive review of the evidence. The following recommendations were taken from the Task Group Report, published in Practical Radiation Oncology 2012 [14]. The level of evidence used for the recommendation is in brackets.

1) Single brain metastasis and good prognosis (expected survival 3 months or more): For a single brain metastasis larger than 3 to 4 cm and amenable to safe complete resection, whole brain radiotherapy (WBRT) and surgery (level 1) should be considered.

Another alternative is surgery and radiosurgery/radiation boost to the resection cavity (level 3). For single metastasis less than 3 to 4 cm, radiosurgery alone or WBRT and radiosurgery or WBRT and surgery (all based on level 1 evidence) should be considered. Another alternative is surgery and radiosurgery or radiation boost to the resection cavity (level 3). For single brain metastasis (less than 3 to 4 cm) that is not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered (level 1). For nonresectable single brain metastasis (larger than 3 to 4 cm), WBRT should be considered (level 3).

2) Multiple brain metastases and good prognosis (expected survival 3 months or more): For selected patients with multiple brain metastases (all less than 3 to 4 cm), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered, based on level 1 evidence. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered (level 3).

3) Patients with poor prognosis (expected survival less than 3 months): Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT (level 3).

Neurocognitive dysfunction The negative impact of whole brain radiation on neurocognitive function as a delayed toxic effect has become an important clinical concern in recent years, again reflecting the fact that increasing numbers of patients have well controlled systemic disease and may live long enough to suffer neurocognitive

toxicity. Equally concerning are data suggesting that the development of micrometastatic disease is associated with an incremental decline in neurocognitive function which predates the appearance of MRI-detectable metastases by at least 1-2 months [15,16]. These data highlight the importance of developing strategies to prevent brain metastases, not simply wait and treat metastases once they are detectable by MRI and/or causing symptoms. The functional balance between up-front whole brain radiotherapy to diminish intracranial relapse versus the neurocognitive deficits induced by whole brain radiotherapy remains an investigational question and a large intergroup trial is attempting to answer it. A small, single institutional study suggested that early neurocognitive deficits may be more frequent with immediate whole brain radiotherapy, but it is not clear whether there was an appropriate balance of patient, tumor and treatment characteristics between the two arms.

Chemotherapy

It has long been recognized that cytotoxic therapy for brain metastasis has little impact[2,7]. Needing both a drug that is effective for treating the tumor type (breast vs. lung vs. melanoma, for example) and adequate brain penetration has been at the root of failed therapies. Drugs with good CNS penetration, such as carboplatin and temozolomide, have been investigated in many small clinical trials as single agents or in combination with radiation, but no meaningful improvements in overall survival have been found. Based on these data, cytotoxic chemotherapy is not recommended for the treatment of brain metastases.

Molecular targeted therapies

The discovery of EGFR activating mutations in non-small cell lung cancer in 2004 was a major breakthrough in this disease when it was shown that targeting the mutation led to rapid and complete responses, although of less than 1 year duration [17]. There are now several small studies and case reports showing that tumors in the brain treated with the EGFR inhibitors can induce tumor shrinkage in the brain, although there is little prospective data. These data are important because they being to provide evidence that the drugs achieve adequate penetration in the brain and tumor, the tumors remain dependent on the EGFR pathway for growth and that the drugs are well tolerated.

Similar data has now been obtained in melanoma brain metastases where BRAF-mutated melanoma brain metastases have been shown to shrink in response to

treatment with vemurafinib (Hoffmann-LaRoche Inc), a BRAF inhibitor that has shown significant activity in $BRAF^{V600E}$ mutated metastatic melanomas outside the central nervous system. Of importance is that responses have been found in brain metastasis patients who were treated at the time of first presentation, as well as in patients treated at the time of progression in the brain after radiation therapy[18,19]. Since it has been shown that vemurafinib has poor brain penetration, the responses are likely due to breakdown of the blood brain barrier to a sufficient degree to enable high enough drug levels within the tumor.

A recent case report of response to vemurafinib in a patient with documented BRAF mutated non-small cell lung cancer is perhaps most informative [20]. Although an 'n of 1', it gives important scientific evidence that the tumor growing in the brain remained dependent on the BRAF pathway rather than losing the dependence when adapted to the brain microenvironment. From a practical clinical perspective, these early pilot studies and case reports demonstrate the importance of including patients with brain metastases in clinical trials of new drugs or drug combinations, especially when selected for molecular driver mutations. These data also highlight a critical question in drug therapy for brain metastases as to whether cells metastasize after they have developed resistance to initial therapy or metastasize early but remain dormant or "protected" behind the blood brain barrier. The EGFR and BRAF cases provide proof of concept that, at least in some cases, the metastatic cell is not resistant to the primary therapy.

At the other end of the spectrum from the EGFR- and BRAF-mutated tumors is HER2 positive (HER2+) breast cancer, an aggressive subtype in which HER2-directed therapy with the monoclonal antibody, trastuzumab, is associated with excellent responses but a high incidence of late development of brain metastases[3,4]. Monoclonal antibodies do not cross the blood brain barrier, thus setting up the brain as a sanctuary site for later metastases in all cancers in which these therapies are used. In an attempt to treat the metastases in HER2+ breast cancer, it was hypothesized that the EGFR/HER-2 dual kinase inhibitor, lapatinib (GlaxoSmithKline, Philadelphia. PA), a drug with good CNS penetration, would be a good option. In 2005–6, a multi-center phase II trial was initiated to study the effects of lapatinib in women with HER2+ breast cancer who developed brain metastases while on trastuzumab. Thirty nine patients were enrolled and 37 patients had received prior whole brain radiation [21]. Several patients had a reduction in tumor volume, one with a good partial response, and 18% of patients had no disease progression over 18 weeks. By traditional clinical trial outcome

measures, this study would be considered a negative trial. However, the study did demonstrate a low level of activity that prompted further investigation. A recent panel proposed practice guidelines for treating HER2+ brain metastases [22], although recognized that there was little level 1 or 2 evidence to definitively guide therapy.

Although lapatinib has not been found to be as effective as trastuzumab alone or improve survival when given in combination with trastuzumab (results presented at ASCO 2014), there are informative data from the studies of laptinib in HER2+ brain metastases. Since lapatinib is a molecularly targeted agent, even limited shrinkage of tumors in the brain suggested that 1) the cells that metastasized to the brain in some patients were not resistant to HER2 inhibition as a result of prior exposure to trastuzumab and 2) the metastatic focus in the brain retained, at least to some extent, its oncogenic dependence on the HER2 pathway. The lack of response in the other patients raised additional questions. Did metastases in these patients develop late, after the development of some degree of trastuzumab resistance? Are there genetic modifications in the tumor cells such that they lose their dependence on the HER-2 pathway? These data also raise the issue of tumor cell dormancy in the brain and its contribution to response or lack of response. These clinical data are invaluable in generating hypothesis driven basic and clinical research, the results of which will enhance the understanding of basic mechanisms of tumor growth and treatment outcome. In addition, the results are profoundly important in the design of future clinical trials of monoclonal antibodies and other drugs that do not readily penetrate the blood brain barrier.

Basic science and translational studies in brain metastasis

Recognizing the alarming increase in brain metastasis in patients with otherwise well controlled systemic cancer, the National Cancer Institute organized a workshop (Biology of Brain Metastasis Workshop, 2008) to generate a set of research priorities that would stimulate integrated scientific and clinical investigation. The following recommendations are taking from the workshop report [2]. To date, limited progress has been made due to the lack of federal funding for the program. The scientific unmet needs remain unchanged and the clinical situation is even more acute.

Research Priorities

A. Genetics of Brain Metastasis

• Comprehensive molecular analysis of brain metastases. Priority should be given to (a) paired analysis of primary tumor and brain metastasis, (b) paired brain and other organ metastases, and (c) primary tumor samples annotated to have metastasized to brain.

• Comparison of molecular profiles among brain metastases from the cancer subtypes (e.g., breast cancer, NSCLC, melanoma, renal cell cancer).

• Identification of novel molecular targets for prevention and treatment of brain metastases.

• Brain metastasis gene discovery and validation via comparative oncogenomics and proteomic approaches.

• Functional evaluation of brain metastasis gene candidates in model systems.

B. Biology of Brain Metastasis

• Delineate pathogenic mechanisms of metastasis to brain.

• Understand the commonalities between systemic disease and metastasis to the brain versus other organs.

• Understand heterogeneity among different brain metastatic lesions to differentiate between indolent and aggressive lesions.

• Investigate issues related to the “stem cell” features of metastasis cell.

• Identify mechanisms underlying tumor cell homing to the brain.

C. Biology of the Blood Brain Barrier

• Identify the cellular constituents of the blood brain barrier and understand

mechanisms of drug transport.

• Develop strategies for modification of the blood brain barrier to enhance drug delivery.

• Develop model systems, including imaging, for preclinical evaluation of drug transport and distribution in the brain.

D. Role of the Brain Microenvironment in Brain Metastasis

• Understand the interaction between the tumor cell and brain stroma.

• Delineate the role of brain stromal cells, astrocytes, and extra-CNS cells in enabling growth of tumor cells in the brain.

• Understand the interaction of tumor, blood vessels, and the brain microenvironment in tumor angiogenesis.

• Identify treatment-induced changes in the brain microenvironment that modify tumor cell growth.

• Identify targets in the brain microenvironment for therapeutic development.

E. Modeling Brain Metastasis in the Mouse

• Develop models for each of the tumor subtypes using both genetically engineered mice as well as human cell line xenograft models.

• Develop reporter lines for use in imaging studies.

• Develop preclinical models for biomarker validation and therapeutic testing.

F. Pharmacology and New Therapies

• Identify and validate compounds that permeate an intact blood brain barrier.

• Modify existing effective, systemically acting compounds for penetration into the

CNS.

• Understand mechanisms of resistance in early versus late brain metastasis.

• Develop and evaluate radio-sensitizing compounds for use with whole-brain radiation and/or radiosurgery.

• Develop methods for quantification of the uptake of compounds into the normal brain, micrometastases, MRI-detectable metastases, and peri-tumoral microenvironment of the brain.

• Develop imaging to quantify drug delivery and molecular targeting in addition to early identification of micrometastases.

G. Translational Research Opportunities

• Perform comprehensive molecular profiling of activated signaling pathways in surgically resected, clinically annotated, brain metastases across tumor types and compare to the primary tumor.

• Develop biomarkers of brain metastasis risk, detection, and response to treatment.

• Develop clinical imaging systems for earlier detection of metastatic foci in the brain.

• Adapt existing clinical trial design to include patients with existing brain metastases and define novel biological and clinical endpoints.

• Understand differential responses among brain metastatic lesions to therapy.

• Develop clinical trials of novel therapies for the prevention of brain metastasis.

• Adapt mouse models for preclinical testing of novel therapeutics and the development of valid endpoints that can be used in clinical studies of brain metastasis.

Resources Needed

A. National Brain Metastasis Working Group

B. Biospecimens

C. Antibodies

D. Bioinformatics

E. Animal Models of Brain Metastasis

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