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THE ROLE OF VASOREGULATORY MECHANISMS IN CENTRAL NERVOUS SYSTEM DAMAGE IN PREMATURE CHILDREN

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ABSTRACT

Astrocytes comprise the major non-neuronal cell population in the mammalian neurovascular unit. Traditionally, astrocytes are known to play broad roles in central nervous system (CNS) homeostasis, including the management of extracellular ion balance and pH, regulation of neurotransmission, and control of cerebral blood flow and metabolism. After CNS injury, cell–cell signaling between neuronal, glial, and vascular cells contribute to repair and recovery in the neurovascular unit. In this mini-review, we propose the idea that astrocytes play a central role in organizing these signals. During CNS recovery, reactive astrocytes communicate with almost all CNS cells and peripheral progenitors, resulting in the promotion of neurogenesis and angiogenesis, regulation of inflammatory response, and modulation of stem/progenitor response. Reciprocally, changes in neurons and vascular components of the remodeling brain should also influence astrocyte signaling. Therefore, understanding the complex and interdependent signaling pathways of reactive astrocytes after CNS injury may reveal fundamental mechanisms and targets for re-integrating the neurovascular unit and augmenting brain recovery.

1. Introduction

The neurovascular unit is a conceptual framework for investigating the mechanisms of central nervous system (CNS) injury and disease [1]. Under normal condition, crosstalk between various types of brain cells including neurons, glia, brain endothelial cells, pericytes, and stem/progenitors take place to maintain CNS homeostasis. However, after CNS injury, disruption of these cell–cell signaling results in the development of acute injury in addition to neuronal damage itself [1- 4]. On the other hand, restoring the neurovascular function may lead to [5- 9] the generation of new blood vessels and facilitating highly coupled neurorestorative processes including neurogenesis and synaptogenesis in the late phase of injury [5- 7]. Collectively, multi-cellular processes within the neurovascular unit can mediate both damage and repair after CNS injury. Of cells in the neurovascular unit, astrocytes comprise 19% to 40% of glial cells in the human brain including neocortical gray matter and white matter [8]. Astrocytes are highly heterogeneous

and pleomorphic, and there are at least two different populations: Protoplasmic astrocytes (gray matter, type-1) and fibrous astrocytes (white matter, type-2). Protoplasmic astrocytes widely distributing in gray matter have a larger size (~50 μm) and more organelles than fibrous astrocytes, and at least one process contacts blood vessels through perivascular endfeet as well as forming multiple contacts with neurons. These astrocytes regulate local blood flow and neuronal homeostasis [9], [10]. Fibrous astrocytes are originated from radial glial cells that are capable of differentiating neurons, astrocytes and oligodendrocytes during brain development, and these astrocytes highly express glial fibrillary acidic protein (GFAP), nestin, and vimentin [11], [12]. Although the specific function remains to be characterized, fibrous astrocytes also contact vessel capillaries like the protoplasmic astrocytes [13]. Generally, elevated GFAP is a common feature of the activation state of astrocytes. In a normal brain, astrocytes play key roles in sustaining CNS homeostasis. Not surprisingly, astrocytes are now known to also play a vital role in how the brain responds to injury and disease. After CNS injury, reactive astrocytes are traditionally thought to impede dendritic and axonal growth by producing inhibitory molecules [14- 16]. However, accumulating evidence now reveal that astrocytes have a wide variety of essential phenotypes, with beneficial and deleterious actions spanning a complex spectrum from the acute stage of injury/disease to the later phases of recovery. The reader is referred to many detailed reviews that rigorously describe these multiphasic astrocyte phenotypes and functions [15], [17- 24]. Here, in this mini-review, we aim to survey primary principles to support the idea that astrocytes comprise a critical source of crosstalk signaling within the neurovascular unit as the damaged brain begins to transition from initial injury into endogenous repair and recovery after CNS injury, including stroke, white matter injury, and spinal cord injury.

2. Methods

2.1 Study design

The ALK in Lung Cancer Trial of brigatinib (ALTA trial; NCT02094573) was an open-label, phase 2, multicenter, international study. The trial evaluated the efficacy and safety of two randomized dosing regimens of brigatinib (Arm A: 90 mg QD and Arm B: 180 mg QD with a 7-day lead-in at 90 mg QD) in patients with locally advanced or metastatic ALK þ NSCLC whose disease had progressed on prior therapy with crizotinib. Patients in the ALTA trial were enrolled from 71 sites, including 15 in the US, one in Canada, 38 in Europe, six in Australia, and 11 in Asia. Eligible patients (18 years of age) had locally advanced or metastatic ALK þ NSCLC, investigator-determined disease progression on crizotinib, 1 measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)29, adequate organ and hematologic function, and Eastern Cooperative Oncology Group (ECOG) performance status.

3. Results

From June 4, 2014 to September 21, 2015, 222 patients were enrolled and randomly assigned to brigatinib in treatment Arm A (*n* ¼ 112) or Arm B (*n* ¼ 110) of the ALTA trial (NCT02094573). The analytical sample in the ITT-PRO population with baseline PRO data and at least one follow-up visit with PRO data included 208 subjects across arm A (n ¼ 105) and Arm B (n ¼ 103). Patient demographic and baseline clinical characteristics of the ITT-PRO sample are shown in Table 2. With the exception of age (Arm A was statistically significantly younger than Arm B), baseline demographic characteristics were balanced between the two dosing arms. It should be noted that the ALK þ NSCLC clinical trial sample tended to be younger and was comprised of more women and more non-smokers relative to the characteristics in the general population of NSCLC patients.

4. Discussion

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The ALTA trial has previously demonstrated the treatment Table 3. benefits of brigatinib for patients with crizotinib-refractory ALK þ NSCLC on traditional cancer outcomes, including ORR and median survival [7]. The clinical data from this more recent data extraction (September 29, 2017) confirmed the durable benefit of brigatinib, in particular the increased benefit of Arm B over Arm A compared with an earlier data cut [6]. Findings based on the EORTC QLQ-C30 functional domains46 found that mean GHS/QoL scale scores were statistically significantly improved over time for patients in both treatment arms. In addition, few patients experienced a meaningful worsening of their GHS/QoL scores. In the context of a severe disease such as NSCLC, the fact that treatment did not result in significant reduction of HRQoL is important, given the potential impact of treatment-related toxicities46. These results are consistent with EORTC QLQ-C30 results based on an earlier data cut from the ALTA study that found HRQoL remained at or above baseline levels and did not differ between arms [6]. The current analysis generated utility scores from the EORTC QLQ-C30 using available algorithms to enable evaluation of patients' health utility. This is important because there is literature suggesting that the generic EQ-5D can have variable levels of sensitivity to detecting change in some health conditions47, and it would be practical to have a suitable algorithm identified to use based on a condition specific scale such as the EORTC QLQ-C30. The current study used two published algorithms (Khan et al. 45 and Longworth et al. 43) in this analysis. The key findings from this exploratory analysis of openlabel phase 2 study data were two-fold. First, the availability of appropriate utility mapping algorithms provided an opportunity to estimate utilities in a study where no health utility measure was administered. The EORTC QLQ-C30 is very widely used in oncology and is a condition-specific PRO that is known to be responsive to detecting changes due to treatment48,49, and may be more sensitive to the cancer patient's experience than a generic preference measure. Because of its widespread use, it could be very useful to have reliable methods for generating utilities from the EORTC QLQ-C30. Application of these mapping methods made it possible to evaluate generated utilities based on two separate algorithms. Consistent results were obtained for utilities derived in this study using the Khan et al. 45 algorithm using the expanded EQ-5D-5L system and Longworth et al. 43 based on the standard EQ-5D-3L measure. Very small numeric differences were observed between the estimates, with Khan et al. 45 algorithm-based estimates approximately 0.01 or 0.02 points lower than those generated based on the Longworth et al. 43 method. This minor variation may potentially be related to differences in the utility measure, patient sample, and/or modeling methods used. The Khan et al. 45 estimates were based on the EQ-5D-5L version, with expanded response levels, that has been noted to have less tendency toward over-prediction of utilities, used only NSCLC population of patients rather than a combination of cancer types, and a BB regression approach to develop the model that may provide better estimation over traditional OLS methods. More accurate prediction for the EQ-5D-5L using the BB model is also corroborated by a recent multi-country survey study comparing alternative statistical approaches to estimating utilities in a sample of 772 patients diagnosed with cancer.

5. Conclusions

Cell–cell signaling between neuronal, glial and vascular compartments provides the signals and substrates for investigating the mechanisms of acute injury and delayed recovery after stroke, brain injury and neurodegeneration [3,113]. The development of therapies to reconnect the diverse communicating signals between multiple cell types will be challenging. During normal brain function, astrocytes are primarily responsible for ionic homeostasis, modulation of synaptic activity and neurotransmission, maintenance of the BBB, and cerebral blood flow regulation and metabolism. After CNS injury and disease, reactive astrocytes represent a complex source of intercellular signals that may impede recovery or potentially contribute to neuroprotection and defense against damaging immune response (Figure 1). The balance between deleterious and beneficial responses warrants careful study. Ultimately, a more nuanced approach may be needed in order to stimulate the beneficial astrocyte program to reconnect and regenerate the entire

neurovascular unit after CNS injury or disease.

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