BRAIN TUMORS – THE ROLE OF MONOCLONAL ANTIBODIES THERAPY AND CHALLENGES OF BLOOD BRAIN BARRIERS

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SOURCE

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KEYWORD

Neuro Oncology, blood-brain barrier, Monoclonal antibodies, Breast Cancer, Brain tumor, Refinement

INTRODUCTION

This review critically reviews the article monoclonal antibodies therapy in neuro oncology The Brain tumors In applying mAb therapy to brain tumors, both expectations and interpretation are seems difficult due to blood-brain barrier (BBB).It prevents the antibodies from entry into the brain but in case of brain tumors their entry is more complex. Brain tumors (the target), antibodies (the magic), how antibodies attack tumor (the bullet) and how they reach it (through blood brain barrier) are reviewed .With this as introduction, practical experience with mAbs for brain tumor targets is by Clinical experience with mAbs in brain tumor therapy indicates that it is less inherently toxic than the conventional therapies and far safer for widespread delivery

Three of the best-studied antibody/target combinations Bevacizumab and GBM**.** It hard to define the effect of the antibody itself on tumor growth bevacizumab primarily reduces edema. Other questions concern response criteria. How to weigh overall survival as opposed to progression-free survival; Rituximab and PCNSL Rituximab targets the common B-cell marker CD20 PCNSL, which is typically a B-cell lymphoma. Trastuzumab and metastatic breast cancer Monoclonal antibodies (mAbs) serve as tumor-specific magic bullets in two ways. As bullets, they would move through the blood to reach and

attack tumor targets and specificity of a single antibody would provide the magic , breast cancer patients respond to systemic mAb treatment, but then metastases appear in the brain**.** Limitations of clinical trials and drawbacks of pre-clinical models interpretation of clinical results difficult - increase in overall or progression-free survival, or simply an improved quality of life, are certainly of benefit to brain tumor patients- delivery strategies and tumor sites

ARTICLE SUMMARY

This article relates to the use of monoclonal antibodies in neuro oncology this therapy is widely used in many cancers (breast, colorectal ,B –cell Lymphoma) but in brain tumors the efficacy the role of blood brain barrier is a special concern . The success against the brain tumors depends on getting past the blood brain barrier to better attack the brain tumor targets .The properties of monoclonal antibodies are-it is highly antibody specific. Of special relevance for antibody therapeutics, FcRn, the Fc receptor that protects antibodies from degradation in serum, is highly expressed on brain vessels. Specific relevance for brain tumor, radiotherapy is thought to alter the BBB in ways that increase antibody access to tumor sites.

Clinical experience reveals with Three Brain Tumor/Antibody Pairs Bevacizumab and GBM. Rituximab and PCNSL Trastuzumab and brain metastasis of breast cancer, the median survival after therapy for GBM lasts for only 15 months or lesser and the concentration of the drug is measurable in CSF and not at the tumor sites ,hence the *Need for new therapies* , In the brain, is of paramount important . What allows entry through blood brain barrier entry of substances from the blood, through BBB is effective at selectively permitting entry of necessary Active transporters that import nutrients and regulatory molecules.

One approach is exploit these transporters .Of special relevance for antibody therapeutics, FcRn, the Fc receptor that protects antibodies from degradation in serum, is highly expressed on brain vessels FcRn-mediated transport is bi-directional, and the predominant direction can be modified experimentally. Whether FcRn might also act to bring antibody into brain tumor sites?

The BBB along with various stage of brain tumors are depicted with two models. The complexity of tumor therapy, difficulty of direct local measurements, limitations of clinical trials and drawbacks of pre-clinical models all complicate interpretation of clinical results. The goals for the future are, as for all tumors, to increase the benefit and reduce the cost of the therapeutics

For the brain, where delivery to micro-tumor is a great challenge, clearer understanding of the nature and role of the BBB, complemented by improved methods for opening or bypassing it is another goal to be accomplished. Summarizing the question that lay ahead is how mAbs can be used effectively in brain tumors whether it depends on antibody itself, a fragment or a synthetic alternative; how the agent will be delivered passively or actively through BBB into the brain

REVIEW LITERATURE

HER-2/neu status is critical, and careful cardiac monitoring is warranted because of cardiac toxicity trastuzumab in the treatment of her-2-positive early breast cancer (1-4) Rituximab in lymphoma A polymorphism in the complement component C1qA correlates with prolonged response following rituximab therapy of follicular lymphoma (5-6)

The use of bevacizumab in colorectal, lung, breast, renal and ovarian cancer: lessons from phase III trials (7-8) CNS complications of breast cancer: Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab.(9-10) . Is the blood-brain barrier relevant in metastatic germ cell tumor. Targeted therapy for neuro-oncology: reviewing the menu. Drug Discov Today (11-12) Chemotherapy for glioblastoma: Lessons learned in the development of targeted therapy for malignant gliomas.(13-14) Concerns about anti-angiogenic treatment in patients with glioblastoma multiform Pathogenesis of primary central nervous system lymphoma: invasion of malignant lymphoid cells into and within the brain parenchyma.

Primary central nervous system lymphoma: biological aspects and controversies in management. Primary central nervous system lymphoma (15-19). Pathology of cerebral metastases Bevacizumab plus irinotecan in the treatment patients with progressive recurrent malignant brain tumours Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. Central nervous system metastases in HER-2-overexpressing metastatic breast cancer: a treatment challenge Cancer therapy using tumor-associated antigens to reduce side effects (20-24)

Managing premedications and the risk for reactions to infusional monoclonal antibody therapy Antibody constructs in cancer therapy: protein engineering strategies to improve exposure in solid tumors. Cancer New animal models to probe brain tumor biology, therapy and immunotherapy: advantages and remaining concerns Animal Models of Brain Tumors. Molecular bases of neuronal individuality: Lessons from anatomical and biochemical studies with monoclonal antibodies Immune therapy for cancer Vaccines for lymphomas: idiotype vaccines inhibition of B cell functions: implications for neurology.(25-32)there are still 40 articles related

ARTICLE STRUCTURE

This article relating to monoclonal antibody therapy in cancer in nuero oncology limitations caused by BBB is a concern .The rationale of this article is to rethink with the findings of **Clinical experience** which indicates that mAbs is less inherently toxic than the conventional therapies and safer for widespread delivery , is likely to increase in overall or progression-free survival and an improved quality of life.

These are certainly of benefit to brain tumor patients if delivery strategies are manipulated and tumor sites targeted. The sub headings target ,magic and bullet is aptly said target are tumors in the brain antibodies (mAbs) would serve as tumor-specific magic bullets in two ways. As bullets, they would

move through the blood to reach and attack specific tumor targets. The specificity of a single antibody provides the magic, new insights are still needed for tumor in the brain .The 3 types of **Brain tumors** – 1] Glioma - primary brain tumors arising within the brain, the high grade glioblastoma multiforme (GBM), most common in adults. 2] primary central nervous system lymphoma occurs in two very different contexts: in patients with AIDS or other forms of immunosuppressed patients . 3]

Metastatic. Blood-borne metastases from other organs are more frequent than primary brain tumors; mostly from tumors of the lung and breast. **The Bullet**: Antibodies can lead to death or arrest of a tumor target, it directly blocks activity of a target molecule by binding to it, others are s of Fc receptors binding. More recently another FcRn receptor, binds to an antibody to protect it from degradation. This leads to the prolonged serum half-life of an antibody

In brain tumor, radiotherapy is thought to alter the BBB in ways that increase antibody access to tumor sites. The entry of mAbs is restricted by BBB in micro brain tumors but as the size of tumor increases the properties change, Success against brain tumors needs passing of mabs through BBB

ARTICLE CRITIQUE

Authority

The author has published related articles in PUB MED online. He tries to find ways to improve monoclonal antibody therapy in Brain tumor as it is less toxic with a view to improve the quality of life and at the same time prevent progression of tumor .The credibility to the author goes with his intent research strategies aiming multiple points of approach .

Accuracy:

The source of the information in the article is a current research. It was also backed up and supported by Clinical findings, recent reference list with these sources cited in-text to support both the literature review and the research itself. The natural evolution of mAb therapy for any tumor at any site is towards redundancy and refinement. Redundancy, is alternative targets are identified and alternative antibodies are prepared against promising targets, old or new. Refinement is that the new antibodies can be designed to solve specific problems: to avoid known cross-reactions or to work by means of alternative effectors mechanisms

Currency:

The journal was published on line in March 1 2011, The research it describes was current and the article cites up-to-date references in the text (ranging from 1996-2009). Therefore the article is current The article includes 74 referenced articles involving areas connected to the subject of this article concerned .It compromises 2 Meta analysis ,one systematic review and other related articles Vaccines for lymphomas: idiotype vaccines article by Houot R, Levy R . Recent advances in blood-brain barrier

disruption as a CNS delivery strategy by Bellavance MA, Blanchette M, Fortin D are some examples of PUB Med which the author has referenced

Relevance:

This was a Research database, which has high credibility in future research context. It was written to inform researchers rather than to entertain or advertise. There is evidence that systemic mAb treatment can benefit patients with brain tumors or other CNS pathology. The nature and site of antibody activity are less clear and It would be relevant to this group for future research The extent to which antibody enters and acts at tumor sites within the brain itself, tumor within the brain, systemic delivery of mAbs is especially relevant. The focus has been on the role of the BBB, to interpret findings for a variety of delivery strategies and tumor sites.

Objectivity:

The information of monoclonal antibody therapy in brain tumor is objectively developed, well supported with a current Clinical findings about the efficacy in various brain tumors research and all evidence are acknowledged and referenced.. The article acknowledged the complexity of the issues discussed in a number of ways. For example, Complex structure and resistance of molecules through Blood brain barrier and supported their research decisions with references to the appropriate and relevant literature. The way the article dealt with the three words bullet magic and target was really superb

Stability:

The article, with its source PMC on line Publication is stable as a resource. Improved clinical trial design will be important for all brain tumors, and supported by more predictive pre-clinical models

ANALYSIS OF GRAPH/IMAGE/TABLE

Table 1 -Tumor/antibody combinations emphasized in the text
Figure 1-Two patterns of tumor growth in the brain. Tumor often grows around blood vessels (left), but some tumors can also infiltrate the brain parenchyma (right).

Figure 2 Distribution of tumor antigens. A tumor cell displays a characteristic combination of components, many of which are also expressed by normal cells. Even though they may not be unique to the tumor, shared antigens can serve as practical tumor targets.
Figure 3 A varied role for the BBB. Possible relationships among tumor (black circles), gadolinium (Gd, black dots), antibody (AB, Y shapes), blood vessels (grey) and the blood-brain barrier (BBB), under different conditions of tumor growth are depicted.

Figure 3 A- 3F relates to different types of models depicting the mAbs and blood brain barrier possibity of acting in brain tumors

RECENT ADVANCES RELATED TO THE TOPIC

Nicholas Butowski, MD, and Susan M. Chang, MD
The large molecular weight of antibodies is likely to result in inefficient drug delivery into the brain because the blood-brain barrier prevents their passage into brain parenchyma. For this reason, mAb therapy is often delivered intra tumorally rather than systemically. Such intra tumoral delivery is generally done via catheter or convection-enhanced delivery methods and might avoid systemic targeting and toxicity. It can be performed into the tumor itself or after resection. In an effort to increase effectiveness, mAbs may be conjugated with drugs, toxins, or radioisotopes. And much is left to discover.

Recent advances in molecular and cell biology have led to a greater understanding of molecular alterations in brain tumors. These advances are being translated into new therapies that will hopefully improve the prognosis for patients with brain tumors. Brain tumors commonly express molecular abnormalities. These alterations can lead to the activation of cell pathways involved in cell proliferation. This knowledge has led to interest in novel anti-brain-tumor therapies targeting key components of these pathways.

Many drugs and monoclonal antibodies have been developed that modulate these pathways and are in various stages of testing. The use of targeted therapies against brain tumors promises to improve the prognosis for patients with brain tumors. However, as the molecular pathogenesis of brain tumors has not been linked to a single genetic defect or target, molecular agents may need to be used in combinations or in tandem with cytotoxic agents. Improved clinical trial design will be important for all tumors, refine the specificity and modifications of the antibody molecule itself. synthesize novel agents, using knowledge of antibody structure and function as a guide

CONCLUSION

Monoclonal antibody therapy in brain tumors ,being less toxic ,highly specific and cost effective will certainly be of benefit to people suffering from brain tumors ,it would not only prevent progression of disease progress but at the same time will increase the quality of life of the patient. The major challenge is the blood brain barrier which does not allow mAbs to cross through it hence a complementary evolution of understanding and technology is needed to improve delivery of therapeutics to tumor masses.

A better understanding of the nature and role of the BBB, complemented by improved methods for opening or bypassing it is necessary and interpreting variety of delivery strategies at tumor sites. In the brain, interpretation of antibody levels is by taking local measurements in cerebrospinal fluid (CSF). This does not take into account anatomic distribution of the antibodies and limitations of clinical trials and drawbacks of pre-clinical models all complicate interpretation of clinical results.

Two parallel approaches for mAbs therapy - One is to refine the specificity and modifications of the antibody molecule itself. The other is synthesize novel agents with the details of antibody structure and

function as a guide. The whole antibody molecule has great value. It has a long half-life and can mediate multiple functions, with new functions and uses that needs to be studied. Still the key mechanisms used by the most successful antibodies in human patients are yet to be established.

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