Monoclonal Antibodies

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Summary

Over the last decades, progress has been made in diagnostic imaging, surgical techniques, radiotherapy, and chemotherapy for the treatment of tumors of the central nervous system. However, the outcome for patients with high-grade gliomas (HGG) has remained essentially unchanged. The use of monoclonal antibodies (MAbs), either unarmed or armed, to target and kill HGG cells has appeared as a prospective adjuvant therapeutic option. The potential of this approach is being investigated in a large number of clinical trials currently in progress for patients with HGG; the encouraging results of some of these phase I/II trials will be summarized here.

In this chapter, we review the critical components for the safe, efficient, and practical implementation of MAb-based immunotherapy for HGG patients as well as the current and future targetable antigens and their corresponding monoclonal antibodies.

Key Words: Glioma; glioblastoma; anaplastic astrocytoma (AA); tumor antigen; monoclonal antibody (MAb); radioisotope; radiotherapy; immunotoxin; clinical study.

INTRODUCTION

High-grade gliomas (HGG) remain resistant to current standard treatments including aggressive surgical resection, external beam radiotherapy, and cytotoxic chemotherapy. The use of monoclonal antibodies (MAbs) has emerged as a potential adjuvant therapeutic modality with the additional advantages of specifically and more effectively targeting and killing tumor cells than conventional adjuvant treatments (radiotherapy, chemotherapy) which are self-limited by cytotoxicity to normal tissues. Although the principle of an antibody-based tumor immunotherapy was published more than 60 yr earlier (1,2), glioma patients were not enrolled in clinical studies until the early 1960s when iv-administered (3)I-labeled polyclonal antibodies were used to target human glioblastoma multiforme (GBM) (3,4) or fibrinogen on intracranial tumors, including gliomas (5). In these studies, the radiation dose that was conveyed to the tumor was sufficient for imaging but not for therapy. It was only with the development of new technology to obtain MAbs with defined affinity and specificity for a tumor-associated antigen (6) (Ag) that the use of antibody-mediated therapy could be realistically envisioned.
The use of MAbs to localize within a tumor in vivo or to function as an immunotherapeutic agent require that several critical factors are met, including: Ag accessibility (external surface of the cell membrane or extracellular localization); Ag stability (lack of shedding; internalization), and sufficient density within the tumor; high specificity, affinity and stability of the targeting MAb; and reasonable MAb transport kinetics within the tumor (dependent on tumor vascularity, vascular permeability, extracellular fluid dynamics, interstitial pressure). The route of administration is also important as the limited permeability of the blood–brain (BBB) and blood–tumor (BTB) barriers restricts the use of systemic injection (7).

In this chapter, we first address the nature of existing MAb constructs, their cytotoxic mechanisms including those that are intrinsic (unarmed MAb) or acquired (armed MAb), and the various administration routes available to optimize target reactivity, as these are some of the most critical components that determine whether a MAb will effectively interact with a targeted tumor. We then review the various targetable HGG Ags and their corresponding MAbs.

ESSENTIAL CRITERIA IN THE PREPARATION OF MONOCLONAL ANTIBODY-BASED THERAPY

Selection of the Monoclonal Antibody Format

The MAb molecular format must be compatible with the biology and macroscopic appearance (size, shape) of the targeted tumor as well as the characteristics of the possible radioactive or toxic conjugate, and the intended administration route (7) (Fig. 1).

MURINE MONOCLONAL ANTIBODIES

Murine MAbs currently constitute the reference standard. The vast majority of MAbs investigated for immunotherapeutic purposes are murine immunoglobulins despite the fact that their clinical use is potentially affected by human anti-mouse antibody (HAMA) formation following systemic injection. Immune complexes consequently accelerate Mab clearance from the circulation, thus lessening their therapeutic potential. More radical responses such as hypersensitivity or allergy are also possible (8,9). MAb-based treatment of high-grade gliomas is, however, frequently approached on a compartmental administration basis. As MAbs eventually find their way into the systemic circulation, the HAMA-induced systemic clearance may confer more advantageous compartment-to-blood and/or tumor-to-blood ratios, which is critical from a therapeutic standpoint (7).

CHIMERIC HUMAN/MOUSE, HUMANIZED, AND FULLY HUMAN MONOCLONAL ANTIBODIES

Chimeric human/mouse MAbs have been engineered to be less immunogenic in humans as only the antigen-binding variable regions are of murine origin (10,11). Chimeric MAbs containing human constant regions of the IgG2 or IgG4 sub-class are more appropriate for MAb-based immunotherapy as Fc-receptor binding is diminished. In consequence, nonspecific binding (i.e., liver, spleen, bone marrow) and activation of antigen-dependent cytotoxicity (ADC) and complement-dependent cytotoxicity (CDC) are decreased (12,13). Moreover, IgG2 chimeric MAbs benefit from the stiffness of the human IgG2 hinge region which enhances the stability of the MAb and, in comparison with murine counterparts, translates into better in vivo tumor localization (14–16). Nonetheless, the presence of murine domains is sufficient to trigger an immune response from the treated host (17,18). Thus, humanized MAbs have been engineered with the aim of further limiting the presence of potentially immunogenic regions. The humanization process consists of the insertion of the murine complementarity-determinin-