The function and composition of B cells in patients with Glioblastoma treated with and without Dexamethasone

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Identify if dexamethasone treatment alters the frequency and functionality of atypic B cells in blood.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON49155

Source
ToetsingOnline

Brief title
GBMdexaB

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Brain Tumor, Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: CCA subsidie

Intervention

Keyword: B cells, Dexamethasone, Glioblastoma

Outcome measures

Primary outcome

In order to quantify and characterize atypic B cells, we have designed a B cell focused panel for analysis by means of mass cytometry that includes the following markers: CD45, CD49d, CD19, CD5, CCR5, CD7, IgD, CD20, IgA, CD25, CD86, CD123, CD21, CD45RA, CD14, CD27, CXCR3, CCR4, CD22, CTLA-4, CD79b, CD95Fas, CD45RO, CD44, CD38, CD73, CD24, CD3, CD9, IgM, HLA-DR, CD71, CD127, and CD16. Data acquisition and analysis will proceed as previously reported (Dusoswa et al., 2019). In addition to this, we will use a smaller panel containing a selection of the markers above with the addition of intracellular IL-10, as reported by others (Wiest et al., 2019).

Secondary outcome

We will collect information regarding potential confounding factors, such as tumor volume, age, body weight, smoking, and other co-morbidities.

Study description

Background summary

Glioblastoma is the most frequent and aggressive form of brain cancer and has a poor prognosis with a life expectancy of 15-17 months due to its rapid and invasive growth. The current standard of care (Stupp protocol); (Stupp et al., 2005) was introduced in 2005 and consist of surgery followed by chemo-radiotherapy (temozolomide) but has only added approximately 3 months to the total life expectancy of patients with glioblastoma. Yet, in all patients the tumor recurs and second line treatment strategies have a very low response rate (less than 20%) with usually a short duration

Currently, there is great interest in targeting the immune system to promote antitumor response as a new means of treating cancers, including glioblastoma. Despite the presence of potential antitumor effector cells within the microenvironment, the growth of glioblastomas persist (Li et al., 2016). A possible explanation for the lack of effective antitumor immune response is the presence of an immunosuppressive microenvironment (Raychaudhuri et al., 2011). This is likely due to a number of factors, including immune checkpoint signaling, T cell exhaustion, glucose depletion, hypoxia, and the presence of immunosuppressive cells, such as regulatory T cells, tolerogenic dendritic cells, and myeloid-derived suppressor cells. Another factor that could contribute to the limited immune response is the low mutational load of glioblastoma, which does not allow for the recognition and removal of cancer cells by the immune system (Charoentong et al., 2017). All of these factors combined have led to the testing of checkpoint inhibitors in clinical trials, which demonstrated that the antigen-specific T cell responses do not always correlate with tumor regression, suggesting that the immunosuppressive microenvironment limits the potential of T cell activation (Lim et al., 2018). While this degree of immunosuppression in glioblastoma appears extreme, it is consistent with the unique immunosuppressive architecture off the brain and may, thus, be more difficult to reverse than with tumors in other locations. Given these barriers to the use of immunotherapy approaches, identifying mechanisms of peripheral and tumoral immunosuppression in glioblastoma is an immediate priority.

Our recent work on biomarker identification in the peripheral blood of glioblastoma patients has led to the identification of a significant increase in the frequency of a subset of B cells characterized by high expression of regulatory-associated molecules such as CD25 and the inhibitor receptor CD95Fas. This atypical B cell subset accounted in a group of glioblastoma patients for more than 10 % of total peripheral blood mononuclear cells. Moreover, correlation network analysis demonstrated a dramatic decrease in correlations of this subset with other immune cell subsets, suggesting a B cell intrinsic cause for their deregulation. Multiple regression analysis allowed us to pinpoint a strong association of dexamethasone administration to higher frequencies of atypical B cells. These atypical memory B cells may well correspond to regulatory B cells, a B cell subset that is recently gaining interest due to its immunosuppressive functions that support immunological tolerance and may also have detrimental effects through contribution to the immune escape of cancer cells (Sarvaria et al., 2017). Mechanisms of suppression include the acquisition of inhibitory ligand expression, phosphorylation of STAT3, and induction of anti-inflammatory cytokines as IL-10 and TGF-β. Regulatory B cell suppressive activity is mainly cytokine-dependent and may affect diverse cell subtypes, including T effector cells, NK cells, myeloid derived suppressor cells and/or tumor associated macrophages. Regulatory B cells may also directly promote tumorigenesis through recruitment of inflammatory cells, and upregulation of pro-angiogenic genes and prometastatic collagenases. Regulatory B cell infiltration has been identified in a variety of solid tumors including, amongst others, ovarian, gastric,

non-small cell lung cancer, pancreatic, esophageal, head and neck, and hepatocellular carcinomas. In glioblastomas, several reports have demonstrated the presence of B cells in the tumor infiltrate, and we have preliminary data that confirms the presence of B cells in surgical material derived from glioblastoma patients. Increasing evidence suggests that recruitment of B cells and acquisition of suppressive activity within the tumor bed may be an important mechanism through which B cells may modulate innate and/or adaptive anti-tumor immunity. Regulatory B cell depletion in the clinic using anti- CD20 antibodies and/or inhibitors of BTK and/or other signaling pathways, may be a useful strategy for augmenting the anti-tumor immune response. Conversely, understanding the reasons causing an increase in regulatory B cell frequencies may open the door to more effective immunotherapies.

Study objective

Identify if dexamethasone treatment alters the frequency and functionality of atypic B cells in blood.

Study design

In order to address a potential causative relationship between dexamethasone administration and the increase of atypical B cell frequencies in the blood of glioblastoma patients, one would have to design a double-blind randomized intervention study where patients would be administered dexamethasone or not. However, such a study cannot be performed in our setting because dexamethasone is a first line therapy for the neurological complaints associated to edema in glioblastoma patients. Importantly, not all glioblastoma patients receive dexamethasone, which allows as to address our question by means of an observational casecontrol study. According to this reasoning, we proposed the following case-control study:
- Case group: 10 consecutive newly diagnosed patients with a clinical indication for of dexamethasone due to their neurological symptoms will be included to this study. Bloodwill be collected at the time of admission to the study (prior to the administration of dexamethasone) and two weeks (± 3 days) later (prior to surgery).
- Control group: The control group will be 10 consecutive newly diagnosed patients that do not require the administration of dexamethasone. The control group will also be sampled at the time of the admission to the study and two weeks (± 3 days) later (prior to surgery).
The duration of the observation will be approximately 2 weeks (the time it takes between diagnosis of a glioblastoma and the surgical intervention).

Study burden and risks

Patients won*t benefit personally of being enrolled in this study. There are no significant risks for patients included in this study. The burden for patients

consists of withdrawing 56 milliliter of blood. Patients do not have to come to the hospital just for the study. Blood drawl is combined with a regular visit. Patients do not have to come to the hospital only for study purposes. There are no direct risks for participating subjects because of the observational nature of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. MRI scan and patient history highly suspicious for a high grade glioma/glioblastoma
2. Indication for surgery as determined by the Multidisciplinairy Brain tumor Board
3. Patients are 18 years or older at first diagnosis

4. Patients are willing and able to give written informed consent

Exclusion criteria

1. No indication for surgery to confirm radiological diagnosis
2. Not able or willing to give informed consent
3. Allergy or intolerance to dexamethasone
4. Diagnosis of glioblastoma could not be confirmed by histological examination

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-03-2020
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	30-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL71359.029.19