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Review

"Security Dilemma": Active Immunotherapy before Versus after Radiation Therapy Alone or Chemo-Radiotherapy for Newly Diagnosed Glioblastoma

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Abstract

Management of glioblastoma should be aggressive and personalised to increase the quality of life. Many new therapies, such as active immunotherapy, increase the overall survival, yet they result in complications which render the search for the optimal treatment strategy challenging.

In order to answer whether the available treatment options should be administered in a specific row, we performed a literature search and meta-analysis. The results show that overall survival among the different treatment groups was equal, while the rates of complications were unequal. After surgery, when active immunotherapy was administered before radiation, radiation and chemotherapy, complication rates were lower.

For newly diagnosed glioblastoma in adults, applying active immunotherapy after total resection but before the other complementary treatment options is associated with lower complication rates.

Keywords

cancer, glioblastoma, immunotherapy, oncology

INTRODUCTION

Glioblastoma is one of the most malignant tumours of the central nervous system (CNS), with a frequency rate between 3 and 5 cases per 100 000 population.[1] The latest classification of the World Health Organization divides glioblastomas into IDH-wild type and IDH-mutant type, both of which are treated with surgery, radiation therapy (RT), and/or chemotherapy (C).[2] The median overall survival (OS) is less than 15 months and depends on various factors, including the tumour type, demographic characteristics, and treatment type.[3]

Current investigations and approaches include immunotherapy in the standard therapeutic plan, which aims to activate the immune system, leading to a better median OS. Among the available types of immunotherapy, active immunotherapy (AI) effectively stimulates the immune system of the patients, thus producing immune cells targeting the tu-

mour. Different protocols of active immunotherapy, in addition to radiation and chemotherapy, have been described.

Until now, however, there are a limited number of studies attempting to combine data with different glioblastoma treatment strategies, including AI, and their effects on outcomes. Therefore, the main goal of this study was to explore how AI affects OS and the rates of complications when each treatment protocol is compared to one another. Additionally, although AI, RT, and chemotherapy help increase the patients' OS, all of them are linked to cytokine release, which represents a leading factor of post-therapeutic complications. This interplay describes the second topic of the current study.

MATERIALS AND METHODS

Complications and cytokines

We aim to study if the sequence of the administered treatment options for glioblastoma may affect the expected results after treatment. We will further try to hypothetically associate the possible differences found with the role of cytokines. This is based on the fact that, after active immunotherapy, extensive secretion of cytokines is related to complications, including neuronal damage, damage to the blood-brain barrier (BBB), DNA, and liver, among others.[4] Such an extensive release of cytokines, often described as the cytokine release syndrome (CRS), is observed after immunotherapy when the tumour cells are being destroyed.[5] Cytokines are also released after "exposure" of tissues to radiation. It is believed that cytokine release is minimized immediately after irradiation (in the first 24 hours), followed by an over-extensive increase of their level in the next few days (24-72 hours), which is probably responsible for the post-radiation complications.[6] Additionally, chemotherapy can increase the cytokines post-therapeutically, inducing symptomatology and complications.[7]

Search strategy

In order to investigate our initial hypothesis, we systematically searched for data on complications and OS after active immune therapy with radiation and chemotherapy in different combinations. We searched Medline, Cochrane, Wiley, and EMBASE databases for articles published between 2001 and 2018. Two independent authors conducted the literature search, using the following MeSH terms and keywords: active immunotherapy, glioblastoma, radiation therapy, chemotherapy, and cytokines. The search was further enhanced by hand-searching the reference lists of the included studies for further eligible studies (the snowball method).

The inclusion criteria were: human studies; articles in English; articles reporting newly diagnosed glioblastoma; articles reporting the OS and complication rates; articles reporting only active immunotherapy in addition to radiation therapy alone or in addition to chemo-and radiation therapy; patients over 18 years of age and articles reporting a concrete row of administered therapies (for instance: Surgery – Vaccination – Radiation Therapy or Surgery – Radiation + Chemotherapy – Vaccination); patients with gross total resection according to the surgical report; clinical studies; clinical trials; and case series.

The exclusion criteria were: non-human studies; articles in other than the English language; recurrent glioblastoma; pediatric patients; articles reporting other types of immunotherapy; case reports; reviews; comments; letters to the editor; articles with insufficient data on the OS or complication rates.

Data extraction and analysis

Data from the included studies were extracted independently by 2 reviewers, and disagreements were discussed with a third author. This way, the possible biases of the analysis were reduced, including measurement bias. The collected data was analysed using the statistical program J.A.S.P. (Jeffreys's Amazing Statistics Program) 0.8.5.1. and SPSS version 25.

RESULTS

Article selection and patient characteristics

Our literature search identified 470 records. After titles and abstract screening, 97 studies were reviewed in full-text. Finally, 16 of them[8-23] were included in this study **(Fig. 1)**. In total, 260 participants were included. The mean age of the subjects was 53.65 years **(Tables 1, 2)**.

Overall survival and complications

Depending on the sequence of the therapeutic options used, the included articles were divided into four groups:

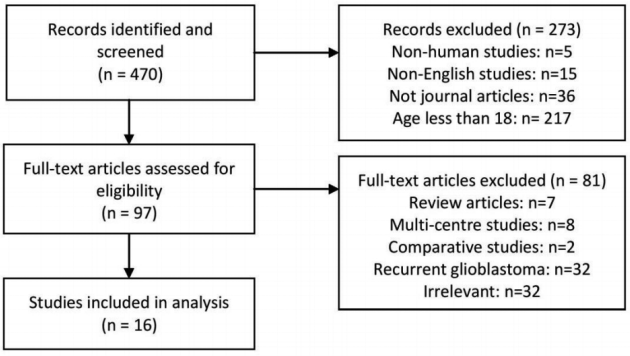

Figure 1. Study selection flow chart.

Table 1. List of articles reporting radiation alone

Study authors	OS months	Age years
Sakamoto et al.[8]	16.5	52
Muragaki et al.[9]	19.8	47.13
Sampson et al.[10]	26	52
Yu et al.[11]	14.79	54.43
Steiner et al.[12]	29.06	53
Chang et al.[13]	15	58.57

Table 2. List of articles reporting radiation and chemotherapy

Study authors	OS months	Age years
Phuphanich et al.[14]	38.4	52
Vik-Mo et al.[15]	25.57	55
Chiocca et al.[16]	15.64	58.6
Ardon et al.[17]	18.3	57
Cho et al.[18]	15.42	61.42
Hashimoto et al.[19]	28	49
Ji et al.[20]	42.3	52
Pellegatta et al.[21]	20.1	54.08
Heimberger et al.[22]	30	51
Sampson et al.[23]	28.27	43.75

1. Surgery (S), then Active immunotherapy (AI), then Radiation therapy (RT) alone.
2. S, then AI, then Radiation with chemotherapy (RTC).
3. S, then RT, then AI.
4. S, then RTC, then AI.

First, we performed an independent t-test on the OS **(Table 3)**. The results showed that all four kinds of combinations lead to the same OS for patients with glioblastoma in the two-tailed test.

Table 3. Independent t-test on overall survival (OS)

		t	df	*p*-value two tailed
OS V2	OS V1	-2.190	8.431	0.058
OS V2 only	OS V1 only	-2.777	3.008	0.069
OS V1	OS V1 only	-2.141	2.009	0.165
OS V2 only	OS V2	-1.268	9.106	0.236

V1: vaccination before radiation therapy+chemotherapy; V2: vaccination after radiation therapy + chemotherapy; V1 only: vaccination before radiation therapy only; V2 only: vaccination after radiation therapy only

Additionally, we performed Bayesian paired t-test for the complication rates, where only the combination 2 (S-AI-RTC) vs. 3 (S-RT-AI) appeared equal, while the rest of the combinations were unequal **(Fig. 2)**. The results of the paired t-tests support the initial hypothesis that the row of therapy administration may play a role in the complication rates observed among the patients.

Potential role of cytokines on outcomes

As mentioned, all treatment options can increase cytokine levels, which can result in complications. Irradiation may play a role in lowering cytokine levels shortly after its administration, and this may account for the low levels of complications if RT is prescribed alone after AI. On the other hand, the complications are expectedly high when RT and Chemotherapy are prescribed before AI, since all

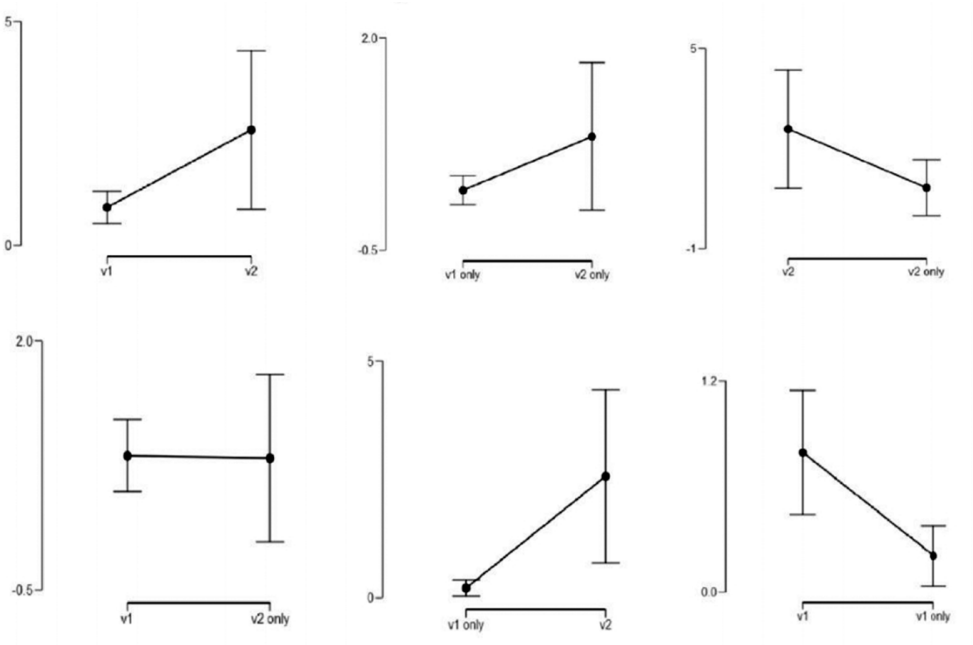

Figure 2. Bayesian t-test – descriptive plots.

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these treatment options cumulatively increase cytokine levels **(Fig. 3)**. If we apply this principle to the second combination, the cytokines of the immunotherapy would be decreased after RT+C, and the post-therapeutical cytokine levels would be mainly a result of the radiation- and chemotherapy. The rates of complications of the third combination do not differ from those of the second one, probably because the levels of cytokines stem from two, rather than three, sources. Namely, in the third combination, the cytokine levels could be the product of AI and RT, while in the second – the product of RT+C. Overall, we can speculate that the cytokine levels may be high if AI is prescribed after radiation with chemotherapy, and low if AI is administered before radiation alone.

Correlation analysis

Finally, correlation analysis was performed comparing the examined parameters (OS, age, and complication rate). According to the results, illustrated in **Table 4**, there is no statistically significant correlation between OS and complication rates, but there is a statistically significant one between OS and age.

DISCUSSION

Glioblastoma is an aggressive neoplasm[24], usually reappearing in a more difficult-to-treat form. This aggressiveness requires new treatment approaches, one of them being immunotherapy. The idea of using immunotherapy for cancer treatment was born not long ago. However, the actual use began in the '60s with the results of an experimental immunization of rodents with irradiated tumour cells.[25] Currently, there are two main immunotherapeutic approaches – passive and active immunotherapy. Passive immunotherapy was introduced in the '80s to '90s for glioblastoma and was followed by many complications. On the

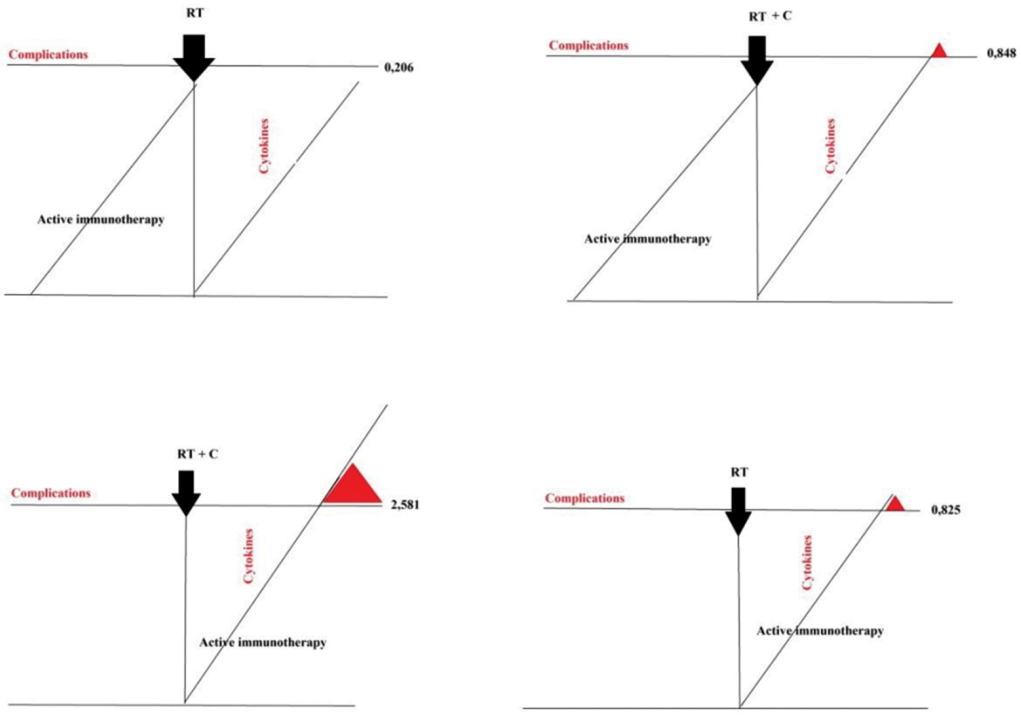

Figure 3. Complications, cytokine levels, and prescribed therapy.

Table 4. Correlation analysis

		Complication rates	Age
Overall survival	Pearson correlation	0.079	**-0.452***
	Sig. (1-tailed)	0.381	**0.034**
	N	17	17
Complication rates	Pearson correlation		-0.264
	Sig. (1-tailed)		0.152
	N		17

*Correlation is significant at the 0.05 level (one-tailed)

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other hand, active immunotherapy appeared to be a more eligible option for patients with glioblastoma.[26]

AI uses different antigens, including tumour parts, protein lysates, or mRNA from the neoplasm, synthetic peptides, and peptides from the MHC class I.[27] AI with autologous tumour cells (ATC) appears to have controversial results. Specifically, a phase I clinical trial reported promising results with three-fourths of patients still alive from glioblastoma, while another study reported no actual benefits.[28,29] AI with dendritic cells (DC) is the most common technique used for glioblastoma. Notably, the use of DC immunotherapy in addition to chemotherapy led to 42% OS at 2 years.[30] Other clinical trials reported a median OS ranging between 9 and 24 months.[31-34]

In general, AI leads to a significant result when applied to smaller tumours.[27] The immune response does not always lead to clinical response; however, it is linked to the complications seen after immunotherapy. These complications are considered to be a part of the cytokine release syndrome, which appears either as a mild condition with fever, fatigue, pain, or rash/skin reaction; or as a severe one, which often leads to death.[35] High levels of inflammatory cytokines can result in a variety of symptoms, such as gastrointestinal dysfunction, including constipation and diarrhea.[36] Severe CRS can present as shock, failure of multiple organs, or acute bleeding. Laboratory tests show abnormalities of the liver enzymes, cytopenias, disturbance of the coagulation factors, and elevated C-reactive protein (CRP). Also, many cases may present with dyspnea, swelling, and neurotoxicity.[35,37-39] The last includes symptoms ranging from mild headache, confusion to a deadly hematoma, hydrocephalus, or seizures. Neurotoxicity is also found among patients following radiation and chemotherapy.[38] Additionally, chemotherapy cycles lead to more severe symptomatology, probably because of the higher cytokine levels.[40]

Overall, the complication symptomatology of all four groups analysed is comparable to that of CRS. Our analysis found that active immunotherapy alone appears to increase the OS of the patients; but in combination with the standard radio- and chemotherapy, it results in high rates of complications. A probable suggestion as a solution to this problem might be the application of AI before the gold standard therapy. This way, the levels of the cytokines could be maintained low, allowing the patients to take the chance of a better survival rate. As a result, lower complication rates can probably be translated to a better quality of life and lower costs of post-therapeutic management.

Readers should consider the weaknesses of this article when applying its results. Complications included in the analysis vary in terms of seriousness, and each study uses different definitions. Another limitation for generalizations is the heterogeneity of AI and chemotherapy types, as well as RT doses included in this study. Our hypothesis about the effect of cytokines on the different rates of complications is theoretical, and further studies are needed to investigate their actual role.

In order to reduce the possibility of measurement, selection, and confirmation bias, we included all the articles that agree with the inclusion criteria, regardless of their clinical outcome. Possible sample bias was reduced by excluding case reports. However, possible bias may stem from the fact that the included studies are based only on the English language and that no unpublished reports were included. Moreover, channelling bias may stem from the age groups included.

CONCLUSIONS

Active immunotherapy can result in lower complication rates if applied after total resection but before radiation or/and chemotherapy for newly diagnosed glioblastoma in adults. This treatment plan, although it does not affect OS, appears safer in terms of complications. Also, cytokines may play a leading role in complication rates. However, this is an observation and hypothesis; thus, further research is needed in order to find the best possible treatment protocol and minimize complication rates.

Conflict of Interest

No conflicts of interest to declare.

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Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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„Дилемма безопасности“: активная иммунотерапия до и после лучевой терапии или химиолучевой терапии при недавно диагностированной глиобластоме

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Резюме

Лечение глиобластомы должно быть агрессивным и персонализированным для повышения качества жизни. Многие новые методы лечения, такие как активная иммунотерапия, увеличивают общую выживаемость, но приводят к осложнениям, которые затрудняют поиск оптимальной стратегии лечения.

Чтобы ответить, следует ли применять доступные варианты лечения в определённом ряду, мы провели обзор литературы и метаанализ. Результаты показывают, что общая выживаемость среди различных групп лечения была одинаковой, в то время как частота осложнений была неодинаковой. После операции, когда активная иммунотерапия проводилась до лучевой, химиолучевой терапии, частота осложнений была ниже.

При недавно диагностированной глиобластоме у взрослых применение активной иммунотерапии после тотальной резекции, но до применения других дополнительных вариантов лечения связано с более низким уровнем осложнений.

Ключевые слова

рак, глиобластома, иммунотерапия, онкология