NovoTTF-100A System as a treatment for Glioblastoma

Amber Morrison
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**Results:** Of the 83 articles screened in the initial search, only 2 met the criteria for review. Both of the selected studies showed prolonged median overall survival for patients treated with NovoTTF-100A therapy, whether that be alone or in combination with other front line treatments. One study was low quality, and the other was very low quality when using the GRADE system.

**Conclusion:** The NovoTTF-100A system is associated with positive outcomes in the treatment of glioblastoma. No significant adverse events were recorded with the use of this therapy, only some localized skin irritation. The NovoTTF-100A therapy does seem to be beneficial to patients with glioblastoma, but further research needs to be done to find out which patients would and would not benefit as much from the therapy.

**Keywords:** NovoTTF-100A, Glioblastoma

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Faculty Advisor: Brent Norris, MPAS, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[redacted]
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Acknowledgements

To Uncle Manny: I am amazed at your strength and courage, you have proven everyone wrong and continue to fight when everything seemed impossible. I hope that in the years to come the treatment protocol for Glioblastoma can be advanced so that it can improve the lives of patients like you.

To my parents: I would not be where I am today without your love and support. I am thankful that no matter what I know I can always come to you for advice. Thank you for pushing me to the best of my abilities and supporting me.

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List of Abbreviations

PRiDe........................................Patient Registry Dataset
GRADE....................................Grading of Recommendations,
                                Assessment, Development,
                                and Evaluation
OS...........................................Overall Survival
KPS.........................................Karnofsky Performance Status
ITT..........................................Intent to treat
TTF..........................................Tumor Treatment Fields
QALY......................................Quality-Adjusted Life-Year
GBM..........................................Glioblastoma

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Appendix A. Epworth Sleepiness Questionnaire and Index
NovoTTF-100A System as a treatment for Glioblastoma

BACKGROUND

Glioblastoma is an aggressive neurological cancer from which most patients do not survive longer than 1-2 years.\(^1\) The current treatment protocol consists of a combination of chemotherapy, surgery for tumor resection, and radiation therapy. The treatment protocol is based on the tumor location as well as the patient’s prognosis and severity at diagnosis.

The NovoTTF-100A system is a new type of therapy that has recently been FDA approved for treatment of supratentorial glioblastoma.\(^2\) It is a helmet device that sends tumor treatment fields (TTF) in alternating intensities of radiofrequency waves through the brain that physically interrupt cell synthesis and division.\(^2,3\) For the device to work effectively in tumor suppression, it is important for patients to wear it continuously, for a minimum of 4 weeks.\(^3\) It is suggested that patients wear the device for 18+ hours a day during each 4-week treatment period.\(^3\) This new treatment method has not been added to the standard of care for patients at this time.
This review will address if the NovoTTF-100A system could be an effective addition to the standard of care for patients with glioblastoma. If the NovoTTF-100A system proves to be an effective method of treatment in patients with glioblastoma, it would be beneficial to have it added to the routine standard of care for patients to have access to it as a primary treatment option.

**METHODS**

An exhaustive medical literature search was completed in June of 2017 using MEDLINE-Ovid, Web of Science, and Google Scholar. The key word included in the search was NovoTTF-100A system. Studies reviewed were narrowed to include studies that enrolled patients with glioblastoma, done within the last 10 years, published in the English language, and conducted on humans. Studies that included treatment of cancers other than glioblastoma were excluded. Selected articles were assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system for overall quality.\(^4\)

**RESULTS**

The medical literature search lead to the review of 83 articles. All articles were screened for inclusion criteria (15 articles were screened
using OVID, 22 articles in Web of Science, and 46 articles in Google Scholar), and 2 articles\textsuperscript{1,3} were selected to meet the stated criteria. One study\textsuperscript{1} is a randomized control trial, that examined the difference between combination chemotherapy and the Novo-TTF100A System, to chemotherapy alone. The second study\textsuperscript{3} is an observational cohort study, that compiled data from a Patient Registry Dataset (PRiDe) of all glioblastoma (GBM) patients who received Novo-TTF as therapy. See Table 1.

**Stupp et al**

This randomized control trial\textsuperscript{1} examined 695 patients, randomizing them in a 2:1 fashion to receive the chemotherapy temozolomide alone or in combination with the NovoTTF-100A therapy. There were 466 patients who received combination therapy, while 229 patients received temozolomide alone. The patients receiving NovoTTF-100A therapy wore the device for >18 hours per day for a total of 5 days in a 28-day cycle. This trial was evaluated with interim analysis, as the trial was terminated due to the overwhelmingly positive results. In the interim analysis, 210 patients were given combination therapy and 105 received temozolomide alone. The interim analysis was completed with these patients after they finished more than 18 months of follow up. The patients were all evaluated using the intent-to-treat (ITT) model.\textsuperscript{1}
The study measured progression-free survival as the primary endpoint in the ITT analyzed population. The secondary endpoint measured was overall survival, in the per-protocol population of 280 patients. Of the 315 patients in the interim analysis, 75% (n=157) were compliant with therapy (average of >18 hours per day for the first 3 months). Median follow up was completed after 38 months, and in the NovoTTF plus temozolomide therapy group median progression-free survival was calculated at 7.1 months (95% CI, 5.9-8.2 months). In the control group with temozolomide alone, the median progression-free survival was calculated as 4.0 months (95% CI, 3.3-5.3 months). The hazard ratio calculated for this difference is 0.64 (99.4% CI 0.42-0.98). The ITT population treated with Novo TTF was also shown to have a longer median overall survival of 19.6 months (95% CI, 16.6-24.4 months), when compared to the chemotherapy alone group of 16.6 months (95% CI, 13.6-19.2 months). These results along with those of the per protocol population can be found summarized in Table 2.

There were no increase in major adverse events recorded during the study with the addition of the NovoTTF to the standard chemotherapy protocol. The main adverse event found was localized skin reactions due to the application of the NovoTFF device directly on
the scalp. Some seizures were reported, but the outcomes were well balanced between the two groups.\textsuperscript{1}

\textbf{Mrugala et al}

This observational cohort study\textsuperscript{2} evaluated 457 patients with GBM in various cancer centers across the US that were using the NovoTTF-100A therapy. All patients that were 18 years or older that used NovoTTF-100A for treatment of recurrent GBM between October 2011 and November 2013 were considered for the data analysis. The patients were not restricted to conjunctive or prior therapies used in addition to NovoTTF-100A. Prognostic variables that were measured were median overall survival (OS), recurrences, age, KPS (Karnofsky Performance Status which measure functional impairment), bevacizumab use, surgeries, as well as adverse events. In addition to the various prognostic variables, compliance was also monitored on a monthly basis according to the daily time Novo-TTF delivered fields.\textsuperscript{2}

Data was analyzed using survival curves in comparison with treatment duration. Median OS was 9.6 months with Novo-TTF therapy, when the best chemotherapy group showed a median OS of 6.0 months. One- and 2-year OS in patients using Novo-TTF therapy were more than double when compared to the best chemotherapy.\textsuperscript{2} The data is summarized in FIGURE 1.
Compliance data began to be collected in January 2013, so it was not available for all 457 patients in the study. It was able to be collected for 63% of the patients (287), and the calculated median daily compliance was 70%. It was found that those who had daily compliance >75% had markedly longer median OS as well (HR 0.43).³

Throughout the duration of the study, no new adverse events were found in comparison with studies that were done previously. The most common adverse event was skin irritation from the Novo-TTF device being placed directly on the scalp.³

**DISCUSSION**

The current standard protocol for patients with recurrent GBM consists of a combination of chemotherapy, radiation, and tumor resection surgery. Recently, there have been studies¹,³ that have proven the NovoTTF-100A system to be an effective treatment for overall survival in glioblastoma patients.

The most current study done by Stupp et al¹ was terminated prior to completion due to the overwhelming results. The NovoTTF-100A system was then FDA approved based on the study’s results, and patients have continued to benefit from its use. While this treatment option has shown to be beneficial, it has not been added to the
standard of care for all GBM patients. This systematic review raises the question if the NovoTTF-100A system could be an effective addition to the standard of care in GBM patients.

Both the Stupp et al study and Mrugala et al study showed an increase in median OS for patients treated with the NovoTTF-100A system. The Stupp et al study, it showed a 38% reduction in death in those patients treated with combination NovoTTF and chemotherapy as well as a 3.1-month increase in median progression-free survival. The Mrugala et al study showed a median OS of 9.6 months in those treated with TTF therapy plus chemotherapy compared to the median OS found in the prior EF-11 trial of 6.6 months. Data from studies has shown that recurrent GBM patients treated with one of the front-line chemotherapy medications temozolomide and surgical resection typically have median OS of 6-9 months.

In a feasibility study that compared TTF alone to the physician’s choice of best chemotherapy, quality of life was analyzed using a survey given every 3 months throughout treatment. The study found that the group that had chemotherapy suffered much higher rates of toxicity, adverse events, and a lower quality of life. Those in the TTF therapy group demonstrated a higher quality of life in the categories of cognitive, emotional, and role functioning. The adverse events recorded in the group with TTF therapy alone was similar to the Stupp
et al study,\(^1\) showing localized skin irritation. The study\(^2\) did not show a difference in overall survival between the 2 groups, but it did show that TTF therapy had similar outcomes to chemotherapy alone. With the significant increase in quality of life, decrease in adverse effects and systemic toxicity, all with similar outcomes in overall survival it shows that the TTF therapy may be a substitute for chemotherapy in patients that choose this option. Patients with poor prognosis may choose to use a more non-invasive therapy in the time that they have to fight the aggressive cancer, and such a choice could be offered by the clinician.

The NovoTTF-100A system does have a positive impact on clinical practice, as it has shown to prolong survival in patients, lead to fewer recurrences, reduced adverse effects in comparison to other treatments typically used, ease of use, and improved quality of life. It is still unclear as to what the ideal patient would be to receive NovoTTF-100A System therapy. It seems that TTF therapy works best when used as a treatment after first recurrence, on patients with a higher KPS scores (>90), and those that have not used bevacizumab as a prior treatment.\(^3\) Compliance is also vital for treatment success, and must be considered with patient selection. The device must be worn continuously for >18 hours a day for at least 4 weeks for the best outcomes.\(^1,3\) There was no difference found in success of
treatment in patients that have had prior surgical debulking procedures.

Cost may also be a concern. On average, the NovoTTF-100A system costs $21,000 a month. The device comes with a treatment kit, and those are leased through the manufacturer Novocure. The median treatment length for the NovoTTF-100A system is roughly 4.1 months, which would total to about $86,000. Medicare does not cover the device, and it was estimated that 1:3 private payers will cover some cost of the device. The device is acquired by the patient when prescribed, so the cost for the healthcare provider is related to the staff training time and teaching the patient how to use the device. In order for providers to prescribe the device, they must participate in a 4-hour training that is held by the manufacturer.

The standard treatment regimen for glioblastoma consists of a combination of chemotherapy, radiation therapy, and surgical resection. One of the primary chemotherapy agents temozolomide (Temodar) can cost from $1,600-$4,600 per month. And additional necessary treatments can cost up to $9,000 per month. These stated costs do not include surgical resection(s), which would add a sizable amount to the total.

There were several limitations to both the Stupp et al\textsuperscript{1} and Mrugala et al\textsuperscript{3} studies. There is a relatively high risk of bias in both
studies, as the company Novocure that manufactured the NovoTTF device funded the studies and had members of the company involved in the study. Many of the studies available are all advertised on their website as well. There was also high variability in the patient populations studied, especially due to the non-controlled, observation aspect of the Mrugala et al study. In addition, there was great variability in the patient’s prior treatments which had the potential to skew some data. Another limitation is that studies did not differentiate if the NovoTFF therapy should be recommended for all patients with recurrent GBM, despite prognosis at diagnosis, recurrence number, disease severity, and previous treatments.

While the Novo-TTF-100A system does seem to have the potential to be beneficial for all recurrent GBM patients, prognostic factors studied need to be more controlled with the addition of NovoTTF to have a more accurate representation of what patients will benefit the most. While it is not likely a study can be done in comparison to a placebo or no treatment group due to ethical considerations of the condition, more studies could be done in comparison to determine if the NovoTTF therapy alone is more beneficial or in combination with chemotherapy. Many of the previous studies have had several compounding variables such as prior
surgery, bevacizumab use, recurrence number, first time treatment, and KPS score, so it is difficult to determine which of those variables may have a favorable or unfavorable outcome in combination with NovoTTF.

CONCLUSION

The NovoTTF-100A System does seem to be an effective treatment for patients with recurrent supratentorial glioblastoma. Studies completed to this date have demonstrated a variety of patients that benefit from the treatment, all with varying prognosis, disease states, and prior or concurrent treatment. The cost of treatment with Novo-TFF-100A will vary patient to patient, as does the cost of the standard treatment regimen. It is possible that the cost of Novo-TTF-100A will be comparable to the standard treatment, which proves that cost should not be a limiting factor for providers introducing the Novo-TTF-100A as a potential treatment option.

While the therapy has shown to be beneficial, more studies with less risk of a bias are needed to distinguish who wouldn’t benefit from the therapy, especially in comparison to the current standard protocol for treatment of GBM. Although the NovoTTF device needs to continue to be reviewed and studied, it has enough evidence that it could be
considered by clinicians in treatment of patients with GBM. There are limited adverse events associated with the device, patients have reported a higher quality of life with the NovoTTF than comparable current treatments, and through the studies discussed in this review it showed to have a prolonged median OS as well as increased progression-free survival.
References


Table 1: Survival Outcome Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Stupp et al</td>
<td>RCT</td>
<td>Serious(^{a,b})</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
<tr>
<td>Mrugala et al</td>
<td>Cohort</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

\(^{a}\) Lack of blinding of participants & data collectors  
\(^{b}\) Trial stopped early  
\(^{c}\) Both studies were funded by the company who made the NovoTTF-100 A System

Table 2. Summary of Findings – Stupp et al\(^{1}\)

<table>
<thead>
<tr>
<th>Population</th>
<th>Median survival for treatment groups in months (95% CIs)</th>
<th>Median survival for control group in months (95% CIs)</th>
<th>HR (CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival in the ITT population</td>
<td>7.1 (5.9-8.2)</td>
<td>4.0 (3.3-5.2)</td>
<td>0.62 (98.7%, 0.43-0.89)</td>
</tr>
<tr>
<td>Overall survival in the per-protocol population</td>
<td>20.5 (16.7-25.0)</td>
<td>15.6 (13.3-19.1)</td>
<td>0.64 (99.4%, 0.42-0.98)</td>
</tr>
<tr>
<td>Overall survival in the ITT population</td>
<td>19.6 (16.6-24.4)</td>
<td>16.6 (13.6-19.2)</td>
<td>0.74 (95%, 0.56-0.98)</td>
</tr>
</tbody>
</table>