TTFields参考资料1

今天 07:11　　未分类

这是文章标题和其中的一页（第7，8页）的部分内容，文中有些细节值得注意。

An Overview of Alternating Electric Fields Therapy (NovoTTF Therapy) for the Treatment of Malignant Glioma

Curr Neurol Neurosci Rep (2016) 16: 8
DOI 10.1007/s11910-015-0606-5

NEURO-ONCOLOGY (LE ABREY, SECTION EDITOR)

An Overview of Alternating Electric Fields Therapy (NovoTTF Therapy) for the Treatment of Malignant Glioma

Kenneth D. Swanson[1] · Edwin Lok[1] · Eric T. Wong[1,2]

Published online: 6 January 2016

◀ **Fig. 3** Computer modeling of electric field distribution within the brain. T1-weighed postgadolinium, T2, and magnetization-prepared rapid gradient-echo magnetic resonance images are imported into Simpleware's ScanIP 7.0 Suite to perform segmentation of various brain structures, including the scalp, skull, dura, cerebrospinal fluid, gray matter, white matter, brainstem, cerebellum, bilateral ventricles, gross tumor volume, and tumor necrotic core. (A) An air-tight volumetric mesh is then generated for finite element analysis using COMSOL Multiphysics. (B) The distribution of electric fields within the brain is inhomogeneous, with the highest fields at the frontal and occipital horns of the lateral ventricles, as well as the medial surface of the glioblastoma

on the equivalent efficacy results and absence of serious associated toxicities, the FDA approved on 8 April 2011 the TTFields therapy for the treatment of recurrent glioblastoma.

The apparent discrepancy in the overall survival rates between the pilot study and the registration trial prompted a series of post hoc analyses of the trial data. First, one of the analyses centered on responders and it showed that five of 14 responders treated with TTFields monotherapy had prior low-grade histology, while none of the seven responders treated with BPC chemotherapy did [41•]. Second, the analysis revealed significantly less dexamethasone use in responders versus nonresponders [41•]. Responders in the TTFields monotherapy group received a median dexamethasone dose of 1.0 mg/day while nonresponders received 5.2 mg/day. A similar difference was also noted in the median cumulative dexamethasone dose of 7.1 mg for responders versus 261.7 mg for nonresponders. In the chemotherapy cohort, the median dexamethasone dose was 1.2 mg/day for responders versus 6.0 mg/day for nonresponders. However, the median cumulative dexamethasone dose was not significantly different (348.5 mg for responders vs 242.3 mg for nonresponder). These data suggest that TTFields efficacy may be influenced by concurrent dexamethasone use, which is a clinically modifiable factor. This finding prompted an in-depth analysis of the dexamethasone effect in the entire trial population.

Applying an unsupervised modified binary search algorithm that stratified the TTFields monotherapy arm of the phase III trial based on the dexamethasone dosage that provided the greatest statistical difference in survival revealed that subjects who used >4.1 mg/day dexamethasone had a markedly shortened mOS of 4.8 months compared with those who received ≤ 4.1 mg/day (mOS of 11.0 months) [42••]. Patients in the chemotherapy arm were observed to have a similar but less robust dichotomization; those who used >4.1 and ≤ 4.1 mg/day dexamethasone had a mOS of 6.0 and 8.9 months, respectively. This difference in overall survival based on dexamethasone dose was unrelated to tumor size but most likely from interference with patient immune effector function. A single institution validation cohort of patients treated with TTFields therapy, using their $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes as a marker of immune competency, suggested the importance of immune competence to TTFields therapy. Importantly, a dexamethasone dosage of >4.0 mg/day was also found to be a poor prognostic factor in newly diagnosed patients who completed radiotherapy [46], supporting the conclusion that dexamethasone can interfere with treatment. With successive increases in dexamethasone dosage, both cohorts reached an inflection point near 8.0 mg/day, after which the rate of survival decreased slowly thereafter. Taken together, dexamethasone exerts a generalized and profound interference on the efficacy of both TTFields and chemotherapeutic treatment against glioblastoma. Therefore, dexamethasone use should be minimized [47].

Transcanial Distribution of Electric Fields from Transducer Arrays

A number of factors, including a medium's electric conductivity and relative permittivity, can affect electric field distrubution. Since each tissue composition is unique, the intracranial structures must therefore be characterized based on their conductivity and permittivity values. The highly heterogeneous architecture of the brain therefore distort electric fields induced by an external source. Electric fields are generally defined as instantaneous changes in electric potential. This change in electric potential results in electromotive disruption of mitotic structures and is therefore the basis for the therapeutic benefit of TTFields [3••]. TTFields therapy for glioblastoma is delivered by two pairs of transducer arrays positioned orthogonally on the shaved scalp, adhered by a thin layer of conductive gel that provides good conductivity (Fig. 2) [48] . TTFields are generated by a battery-powered alternating current generator, operating at 200 kHz, with maximum voltage alternating from +50 to –50 V. To obtain a comprehensive model of the electric fields distribution in the brain, computer modeling can be performed using co-registered patient Digital Imaging and Communications in Medicine (DICOM) datasets from T1-weighed postgadolinium, T2, and magnetization-prepared rapid gradient-echo magnetic resonance images. Previously, Lok et al. [49•] have shown a heterogeneous distribution of electric fields in the brain, and the regions adjacent to the ventricular horns had a particularly high electric field intensity (Fig. 3). This is likely due to the higher electric conductivity of cerebrospinal fluid (CSF) than the surrounding tissues, which behaves like the terminal of a capacitor, with the surrounding tissues functioning much like a dielectric between conductive terminals. Since a dielectric medium generally retains charge, the rate at which the medium is able to collect and retain the charge is defined by its conductivity and relative permittivity. At 200 kHz, the effect of permittivity is overwhelmed by the conductivity of the medium [50]. Furthermore, the rate at which the medium is able to collect and retain charges is frequency dependent. At high

frequencies, each medium has a unique capacitive reactance characteristic of the medium's conductivity, and thus the medium only has limited time to collect a finite amount of charge and retain it before the field collapses as the polarity changes direction, thereby discharging the initially retained charge before repeating the process. Since CSF has a low permittivity value compared with its surrounding tissues, it is a poor dielectric medium and thus charges will migrate through the fluid layer at a much faster rate with minimal charge retention. This explains why most of the CSF exhibits very low electric field intensity. However, this is not true at the interface between CSF and its adjacent brain tissue. The computed electric field distribution revealed that the ventricular horns exhibit a higher electric field intensity than the rest of the CSF space. This is likely due to the geometry of the region coupled with increased electric potential and reactance causing large field changes.

The electric properties of gliomas are likely to vary among patients, depending on their tumor composition. Tumors with larger necrotic cores are likely to exhibit higher field intensities in the gross tumor volume owing to the capacitive reactance as explained above. In contrast, tumors with smaller or no necrotic core will likely exhibit lower field intensities at the center of the volume due to absence of a conductive medium to act as an electric current source. This may become clinically relevant owing to the increased requirement for time of exposure to TTFields as the outer layers of the gross tumor volume is treated slowly because of lower field intensities.

The Use of TTFields Therapy in Clinical Practice

The post-FDA-approved use of TTFields therapy in routine clinical practice may differ from that in the registration trial because of the stringent entry criteria built into the trial. Therefore, a Patient Registry Dataset (PRiDe) was developed in an effort to capture pertinent clinical practice data. This dataset consisted of 457 patients from 91 treatment centers in the US. Patients treated and captured in PRiDe had a mOS of 9.6 months compared with the 6.6 months in the TTFields monotherapy arm in the registration trial [44••, 51]. The 1-year OS rate was also longer at 44 % compared with 20 %, respectively [44••, 51]. The difference in survival characteristics is most likely due to the higher proportion of patients treated with TTFields at first recurrence in PRiDe (33 %) than that in the registration trial (9 %). Treatment at an earlier time point in the process of disease progression may provide a higher efficacy than treatment at a later time point. Absence of prior bevacizumab usage was also favorable [51]. However, the heterogeneity in the adjunctive treatments used in conjunction with TTFields therapy in the PRiDe dataset, which included cytotoxic chemotherapy, bevacizumab, or even alternative medicine that were not adequately captured, is an important caveat that makes it statistically noncomparative with the TTFields monotherapy arm in the registration trial.

Efficacy of TTFields Therapy for Newly Diagnosed Glioblastoma

TTFields therapy is currently being tested in glioblastoma patients after their initial radiotherapy and concomitant daily temozolomide. In this phase III trial, 700 patients were randomized 2:1 to received either TTFields plus adjuvant temozolomide or temozolomide alone, respectively [52, 53]. The primary end point was PFS. In a prespecified interim analysis of the first 315 patients after a minimum follow-up of 18 months, the intent-to-treat cohort that received TTFields plus temozolomide had a longer PFS than the cohort treated with temozolomide alone (median 7.1 vs 4.0 months, HR 0.6; log-rank $p=0.0014$). The mOS also favors the TTFields plus temozolomide group (19.6 vs 16.6 months, HR 0.75; log-rank $p=0.034$), as well as the per-protocol population that started the second cycle of treatment (20.5 vs 15.5 months, HR 0.67; log-rank $p=0.0072$).

The trial population had no unexpected adverse events. Grade 3 and 4 hematological toxicities between the TTFields plus temozolomide and temozolomide alone cohorts (12 % vs 9 %), gastrointestinal disorders (5 % vs 2 %), and convulsions (7 % vs 7 %) were not significantly different. Only scalp reaction was more common than those that had temozolomide only.

Conclusion and Future Directions

TTFields interferes with α-/β-tubulin and septin 2, 6, 7 heterotrimer function in tumor cells during mitosis. A phase III clinical trial has shown a favorable toxicity profile in recurrent glioblastoma and promising efficacy data in newly diagnosed glioblastoma. Computer modeling showed inhomogeneous distribution of electric fields within the brain. Future investigations will likely include combination treatments, including immune therapies, that can potentially boost the existing efficacy of TTFields monotherapy.

Acknowledgments Supported in part by the "A Reason To Ride" research fund.

Compliance with Ethics Guidelines

Conflict of Interest Edwin Lok declares that he has no conflict of interest. Kenneth D. Swanson has received grants from Novocure, Inc. Eric T. Wong received an unstricted grant for laboratory investigation and an honorarium for a lecture from Novocure.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

<译文>

小标题：换能器阵列电场的经颅分布

许多因素，包括介质的电导率和相对介电常数，都会影响电场分布。由于每种组织成分都是独特的，因此必须根据其电导率和介电常数来表征颅内结构。因此，大脑的高度异质结构扭曲了由外部来源诱导的电场。电场通常被定义为电势的瞬时变化。这种电位变化导致有丝分裂结构的电动破坏，而这正是TTFields治疗益处的基础[3-]。胶质母细胞瘤的TTFields治疗是通过两对换能器阵列提供的，这两对换能器排列或垂直放置在剃光的头皮上，由一层提供良好导电性的导电凝胶粘附（图2）[48]

TTFields由电池供电的交流电流发生器产生，工作频率为200kHz，最大交流电压为+50V至-50V。为了获得大脑中电场分布的综合模型，可以使用来自T1加权钆造影剂增强图像 （post gadolinium）、T2和预磁化快速梯度回波磁共振图像的共同注册患者医学数字成像和通信（DICOM）数据集进行计算机建模。此前，Lok等人[49.]已经显示了大脑中电场的不均匀分布，与心室激素相邻的区域具有特别高的电场强度（图3）。

这可能是由于脑脊液（CSF）的电导率高于周围组织的电导率，其行为就像电容器的端子，而所围组织的功能就像导电端子之间的介电介质。由于介电介质通常保持电荷，因此介质能够收集和保持电荷的速率由其电导率和相对介电常数决定。在200kHz时，介电常数的影响被介质的电导率所淹没[50]。可以说，介质能够收集和保持电荷的速率取决于频率。在高频段，每种介质都有一个独特的容抗
介质导电性的特征，因此介质只有有限的时间来收集有限量的电荷，并在电场随着极性改变方向而崩溃之前将其保留，从而在重复该过程之前释放最初保留的电荷。由于与其周围组织相比，CSF的介电常数较低，因此它是一种较差的介电介质，因此电荷将以更快的速率迁移通过流体层，同时电荷保持率最低。这就解释了为什么大多数CSF表现出非常低的电场强度。然而，在CSF与其相邻脑组织之间的界面上，情况并非如此。计算的电场分布显示，心室激素表现出比CSF空间其他部分更高的电场强度。这可能是由于该区域的几何形状与增加的电势和电抗相结合，导致了大的场变化。
胶质瘤的电学性质可能因患者的肿瘤成分而异。如上所述，由于电容反应，坏死核较大的肿瘤在总肿瘤体积中可能表现出更高的场强。相反，由于缺乏用作电流源的导电介质，具有较小或没有坏死核心的肿瘤可能在体积中心表现出较低的场强。这可能与临床相关，因为由于较低的场强，肿瘤总体积的外层处理缓慢，对TTFields暴露时间的要求增加。
<译文到此结束>

我们有没有医生学者研究一下肺的电场分布情况，用计算机大数据建立电场分布模型，以造福广大肺癌患者？

从文中可知，针对脑胶质母细胞瘤，作者使用的信号发生器输出是100V峰峰值（+50V~-50V），200KHz。所以较高电压供电的功率放大器是必须的。
此文对脑部电场分布的解释是读过的文献中条理最清晰的。
顺便提一下文中的换能器阵列，曾在另外一篇文献中看到说是一种高级的压电陶瓷，PMN-PT，介电常数非常高。价格不菲，是不是使用更高电压就能起到同样的效果呢？