Alternating electric fields (AEFs)

Alternating electric fields, also known as tumor treating fields (TTFields), are low intensity (1-3 V/cm), intermediate-frequency (100-300 kHz), alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor.

Devices

see NovoTTF 100A device

Therapeutic mechanism

It works by perturbing tumor cells during mitosis as they enter anaphase leading to aneuploidy, asymmetric chromosome segregation and cell death with evidence of increased immunogenicity. Clinical trial data have shown equivalent efficacy when compared to salvage chemotherapies in recurrent disease. Responders were found to have had a lower dexamethasone usage and a higher rate of prior low-grade histology.

Rehman et al in a article provides essential information regarding the supposed therapeutic mechanism as well as modes of potential tumor resistance to such novel therapy, delineating future perspectives regarding basic science research on the issue [1].

TTFields have no effect on non-dividing cells. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. It has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, meho have exhausted surgical and radiation treatments [2].

The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes [3].

There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept [4].

Indications

Alternating electric fields-also known as tumor-treating fields (TTFs)-represent an entirely original therapeutic modality with preliminary studies suggesting comparable, and at times improved, efficacy to standard chemotherapeutic agents in the treatment of Glioblastoma recurrence.

In a phase III clinical trial for Glioblastoma recurrence, TTFields were shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely

because the subjects' tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. Therefore, it is likely that the efficacy of TTFields can be increased by combining it with other anti-cancer treatment modalities [5)].

Ongoing and future trials will evaluate TTFields in newly diagnosed glioblastoma, solid tumor brain metastases, nonSmall-cell lung cancer, and ovarian and pancreatic cancers [6)].

Adverse effects

AEFs were shown to have limited systemic adverse effects, with the most common side effect being contact dermatitis on the scalp at the sites of transducer placement. This study prompted FDA approval of the NovoTTF-100A system in April 2011 as a standalone therapy for treatment of Glioblastoma recurrence refractory to surgical and radiation treatment.

Dexamethasone exerted profound effects on both TTFields and chemotherapy efficacy resulting in lower patient OS. Therefore, global immunosuppression by dexamethasone likely interferes with immune functions that are necessary for the treatment of glioblastoma [7)].

Case series

2015

Wong et al. treated a series of patients with NovoTTF 100A and bevacizumab alone (n = 34) or in combination with a regimen consisting of 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) (n = 3). Compared to the former cohort, the latter cohort exhibited a trend for prolonged overall survival, median 4.1 (0.3-22.7) months versus 10.3 (7.7-13.6) months respectively (P = 0.0951), with one experiencing an objective response with a 50% reduction in tumor size on magnetic resonance imaging despite possessing a larger tumor size at baseline and more severe neurologic dysfunction than the median for either group. These observations illustrate the possibility of improving survival and achieving a response in patients with end-stage Glioblastoma recurrence by biasing the tumor toward anti-tumor immunologic response with a combination of NovoTTF-100A and TCCC, as well as the continuation of bevacizumab in order to limit dexamethasone use due to its global immunosuppressive effect on the patient [8)].

2014

Wong et al. analyzed the characteristics of responders and nonresponders in both cohorts to determine the characteristics of response and potential predictive factors. Tumor response and progression were determined by Macdonald criteria. Time to response, response duration, progression-free survival (PFS) ± Simon-Makuch correction, overall survival (OS), prognostic factors, and relative hazard rates were compared between responders and nonresponders. Median response duration was 7.3 versus 5.6 months for NovoTTF-100A and BPC chemotherapy, respectively (P = 0.0009). Five of 14 NovoTTF-100A responders but none of seven BPC responders had prior low-grade histology. Mean cumulative dexamethasone dose was 35.9 mg for responders versus 485.6 mg for

nonresponders in the NovoTTF-100A cohort (P < 0.0001). Hazard analysis showed delayed tumor progression in responders compared to nonresponders. Simon-Makuch-adjusted PFS was longer in responders than in nonresponders treated with NovoTTF-100A (P = 0.0007) or BPC chemotherapy (P = 0.0222). Median OS was longer for responders than nonresponders treated with NovoTTF-100A (P < 0.0001) and BPC chemotherapy (P = 0.0235). Pearson analysis showed strong correlation between response and OS in NovoTTF-100A (P = 0.0002) but not in BPC cohort (P = 0.2900). Our results indicate that the response characteristics favor NovoTTF-100A and data on prior low-grade histology and dexamethasone suggest potential genetic and epigenetic determinants of NovoTTF-100A response [9].

Three patients with Glioblastoma in whom the fields were adjusted at recurrence and the effects of each adjustment. Turner et al. believe there may be a higher risk of treatment failure on the edges of the field where the field strength may be lower. The first patient underwent subtotal resection, radiotherapy with temozolomide (TMZ), and then began NovoTTF Therapy with metronomic TMZ. She had good control for nine months; however, new bifrontal lesions developed, and her fields were adjusted with a subsequent radiographic response. Over the next five months, her tumor burden increased and death was preceded by a right insular recurrence. A second patient underwent two resections followed by radiotherapy/TMZ and NovoTTF Therapy/TMZ. Six months later, two new distal lesions were noted, and he underwent further resection with adjustment of his fields. He remained stable over the subsequent year on NovoTTF Therapy and bevacizumab. A third patient on NovoTTF Therapy/TMZ remained stable for two years but developed a small, slow growing enhancing lesion, which was resected, and his fields were adjusted accordingly. Interestingly, the pathology showed giant cell Glioblastoma with multiple syncitial-type cells. Based on these observations, we believe that field strength may play a role in 'out of field' recurrences and that either the presence of a certain field strength may select for cells that are of a different size or that tumor cells may change size to avoid the effects of the TTFields [10].

2007

In 10 patients with Glioblastoma recurrence (Glioblastoma). Median time to disease progression in these patients was 26.1 weeks and median overall survival was 62.2 weeks. These time to disease progression and OS values are more than double the reported medians of historical control patients. No device-related serious adverse events were seen after >70 months of cumulative treatment in all of the patients. The only device-related side effect seen was a mild to moderate contact dermatitis beneath the field delivering electrodes.They conclude that TTFields are a safe and effective new treatment modality which effectively slows down tumor growth in vitro, in vivo and, as demonstrated here, in human cancer patients [11].

Case report

A patient with recurrent cystic glioblastoma who received add-on TTFields therapy due to an incomplete response to single-agent bevacizumab. After 6 cycles of therapy, a resolution of cystic enhancement was noted, together with reduction of the tumor cyst and resolution of most of the cerebral edema in the surrounding brain. However, the patient also suffered from relapsed disease at locations distant from the original glioblastoma and the corresponding radiation fields received at initial diagnosis. We conclude that combination TTFields and bevacizumab therapy is safe and may be

efficacious for patients with Glioblastoma recurrence. A further study would be needed to determine the relapse pattern and the distribution of the electric fields in the brain [12)].

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