Tumor Treating Fields—An Emerging Cancer Treatment Modality

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Tumor treating fields (TTFs) are an evolving new anticancer modality. The U.S. Food and Drug Administration has approved the first device, the NovoTTF-100A™, that uses this technology and is indicated for use in progressive glioblastoma multiforme after standard therapies have failed. Promising clinical trial results will likely lead to expanded uses in primary brain tumors and other cancer types. This article will review the concept of TTFs and their mechanism of action, and overview the TTF device and its approved usage.

The U.S. Food and Drug Administration (2011) approved the NovoTTF-100A™ system as a treatment for recurrent glioblastoma multiforme (GBM) in April 2011. NovoTTF-100A is the first approved device that uses tumor treating fields (TTFs), a novel technology that delivers alternating low-intensity and intermediate-frequency electrical fields to a tumor. NovoTTF-100A was approved for patients with recurrent glioblastoma multiforme as an alternative treatment modality to chemotherapy after surgical and radiation options have been exhausted (Novocure, 2012).

TTFs cause apoptosis (cell death) during mitosis, disrupting the assembly of the spindle apparatus in metaphase, and preventing the parent cell from dividing into two daughter cells during telophase (Kirson et al., 2004). The dividing cells of the hematopoietic system are not affected by TTFs; muscles that surround the bone and marrow act as an effective electrical field shield (Kirson, Giladi, et al., 2009). TTFs do not stimulate nerves or muscles; the frequency is too high to cause membrane depolarization. Also, it does not heat up the tissue because the frequency is too low to cause dielectric (electronic) heating (Pless & Weinberg, 2011). NovoTTF-100A is a portable, battery-operated device that delivers TTFs to patients via electrodes placed on the scalp (see Figures 1 and 2).

Glioblastoma

In 2013, about 23,130 people will be diagnosed with a malignant tumor of the brain or spinal cord, and an estimated 14,080 will die from these tumors (American Cancer Society, 2013). Glioblastoma multiforme is the most common and aggressive primary malignant brain tumor in adults. Median survival is about 15 months from diagnosis, with most tumors reoccurring within nine months of initial treatment (Stupp et al., 2005).

Standard initial therapy for glioblastoma multiforme includes maximal surgical resection and combined temozolomide chemotherapy with radiation, followed by at least six cycles of monthly adjuvant temozolomide (National Comprehensive Cancer Network [NCCN], 2013). Treatment options are limited for patients with recurrent glioblastoma multiforme. At the time of reoccurrence, re-resection and re-irradiation are options for some patients. Chemotherapy agents have limited effectiveness because of the blood-brain barrier, a tightly woven mesh of endothelial cells, astrocytes, and transmembrane proteins that line the vessels of the central nervous system. The barrier restricts diffusion of bacteria and other large or water-soluble molecules from the bloodstream into the brain. As a result, most chemotherapy agents cannot penetrate the brain. Agents that are used at reoccurrence include temozolomide, the nitrosoureas (carmustine and lomustine), carboplatin, irinotecan, and procarbazine. In May 2009, bevacizumab was approved and frequently is incorporated into recurrent glioblastoma multiforme treatment.
regimens either alone, or in combination with chemotherapy (NCCN, 2013). Clinical trials remain an important option, with many focusing on molecular pathways and tyrosine kinase inhibition. Unfortunately, treatment response rates for recurrent glioblastoma multiforme are dismal (< 10%), and progression-free survival at six months is less than 20% (Stupp et al., 2012). Quality of life (QOL) must be considered for patients with such a poor prognosis. Clinical trials, chemotherapy, and biotherapies come with a multitude of side effects, including nausea, vomiting, constipation or diarrhea, fatigue, and myelosuppression. Although uncommon, bevacizumab can cause serious side effects, including bleeding, hypertension, increased risk of stroke, delayed wound healing, and abdominal perforation (Genentech, 2013). The lack of side effects from NovoTTF-100A (primarily only scalp irritation from the electrodes) makes it an attractive treatment option in this clinical scenario.

Patient Considerations

The Novocure device may not be the best option for all patients; patients must maintain a close-shaven head and wear the device daily for at least 18 hours. The device has an internal electronic file that logs the time the patient is wearing the device; longer survival was observed in patients who wore the device at least 75% of the time versus those who wore it less (7.7 months versus 4.5 months) (Novocure, 2012). Patients with active implanted medical devices such as pacemakers, defibrillators, programmable shunts, or deep brain stimulators cannot use the device. Certain skull defects, such as a missing piece of bone without replacement or the presence of bullet or shrapnel fragments, also may be a contraindication to therapy. Calculated from magnetic resonance imaging, a software program maps out the placement of two pairs of adhesive pads, called transducer arrays, in a patient-specific colored-coded layout maximizing delivery of TTFs to the tumor (see Figure 3). The array layouts are color coded so that they are placed in the same position each time they are removed and reapplied. Patients and caregivers are taught to replace the arrays once or twice weekly and to maintain meticulous skin care. They also receive comprehensive training from a Novocure device support specialist regarding device operation and troubleshooting. Technical support is available to patients and caregivers 24 hours per day, seven days per week. A reimbursement support team works with each patient individually to ensure coverage for the system. Patients also may qualify for financial assistance. Patient education information and videos are available online at www.novottftherapy.com.

Future Implications

Clinical trials have demonstrated that combination TTFs with chemotherapy results in increased chemotherapy sensitivity and efficacy without increased toxicity (Kirson, Schneiderman, et al., 2009). A phase III trial (NCT 00916409) for newly diagnosed patients with glioblastoma multiforme treated with combination temozolomide chemotherapy and TTFs is being conducted by the National Cancer Institute (2013). TTFs have the potential to inhibit metastases, and promising results
Case Study: NovoTTF-100A™

J.U. is a 54-year-old right-handed man who presented at his local emergency room with complaints of severe headache, right-sided weakness, and word-finding difficulty. Magnetic resonance imaging revealed a large left parietal lesion. He underwent gross total resection, and the pathology was consistent with glioblastoma multiforme.

After recovering from surgery, J.U. received standard therapy with daily oral temozolomide chemotherapy and involved field radiation therapy for six weeks. He was maintained on adjuvant temozolomide for 14 months until he developed progressive weakness and aphasia and was found to have disease progression. He began therapy with IV bevacizumab and irinotecan every two weeks, but this was discontinued after several months because of the development of nephrotic syndrome and excessive fatigue. Monotherapy with NovoTTF-100A™ device began. J.U. developed scalp soreness and irritation requiring intermittent (1–2 days) treatment device breaks and was educated to slightly alter the placement of the transducer arrays to facilitate healing. He continued therapy with NovoTTF-100A and enjoyed working part-time and traveling with his family on an extended vacation. After 10 months, J.U. again demonstrated disease progression and was switched to single-agent carmustine chemotherapy.

were seen in early trials with lung cancer and melanoma and with breast cancer-related skin lesions (Pless & Weinberg, 2011; Salzberg, Kirson, Palti, & Rochiltz, 2008).

References


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