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Tumor Treating Fields in combination with paclitaxel in recurrent ovarian carcinoma: Results of the INNOVATE pilot study

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ABSTRACT

Background. Tumor Treating Fields (TTFields) are an anti-mitotic therapy comprising continuous delivery of low-intensity alternating electric fields at intermediate frequencies to the tumor region by a home-use medical device.

Methods. The INNOVATE (EF-22) Study was a phase 2, single arm clinical trial, which tested the safety and efficacy of TTFields (200 kHz) in combination with weekly paclitaxel (weekly for 8 weeks and then on days 1, 8, 15 of each subsequent 28 day-cycle; starting dose 80 mg/m^2) in 31 patients with recurrent, platinum-resistant ovarian carcinoma. The primary endpoint was safety and secondary endpoints included OS, PFS and RR.

Results. Median age was 60 (range: 45–77), 24 patients (77%) had serous histology, 16 patients (52%) ECOG score 0 and 15 (48%) ECOG 1, the median number of prior chemotherapy lines was 4 (range: 1–11). All patients received prior platinum-based chemotherapy and 30 (97%) received prior taxanes. No serious adverse events related to TTFields were reported. There was no increase in grade 3–4 adverse events compared to the frequency of such events reported in the literature with single agent weekly paclitaxel. Twenty-six patients (84%) had the expected TTFields-related dermatitis but only one patient permanently discontinued TTFields due to dermatitis. The median PFS was 8.9 months, 7 patients (25%) had partial response and the clinical benefit rate was 71%. The median overall survival was not reached: the one-year survival rate was 61%.

Conclusion. TTFields combined with weekly paclitaxel were safe in platinum-resistant recurrent ovarian cancer and warrants evaluation in a randomized phase 3 trial.

1. Introduction

Ovarian cancer is the second most common gynecologic malignancy and the eighth cause of death from cancer in women worldwide (239,000 cases and 152,000 deaths) [1]. While most patients achieve a complete remission, the majority (80–85%) will recur. At the time of recurrence, the platinum-free interval predicts response to further platinum-based treatments [2,3]. Almost all patients will ultimately develop a platinum-resistant disease, with about 25% demonstrating resistance at the time of first recurrence [4].

There are several initial treatment options for platinum-resistant recurrent tubo-ovarian cancer. Weekly paclitaxel, which leads to relatively high response rates, could be administered as a single agent or in combination with bevacizumab [5–7]. For patients who previously progressed on paclitaxel following disease progression or are not candidates for the treatment, pegylated liposomal doxorubicin (PLD) is often the treatment of choice [8, 9], with response rates below 20%. Additional agents, including gemcitabine and topotecan, appear to have a similarly low response rate and efficacy [7,10–12]. Limited data suggest benefit from further lines of treatment [13], while the reported OS after the first platinum-resistant relapse prior to multiple treatment lines remains around 12 months [14].

Tumor Treating Fields (TTFields) are an anti-mitotic therapy based on the delivery of low-intensity (1–3 V/cm) alternating electric fields at intermediate frequencies of 100–300 kHz to the region of the tumor. TTFields interfere with the normal mitotic process of cancer cells at multiple stages, predominantly inhibiting the normal polymerization process of the mitotic spindle at metaphase, and disrupting the physiological function of multiple organelles due to cytoplasmatic dislocation towards the end of telophase [15–17]. TTFields are administered non-invasively by means of transducer arrays applied to the skin surrounding the tumor and connected to a small, portable, medical device. The size of transducer arrays and their positioning on the skin intend to ensure therapeutic level intensities throughout the region where the

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tumor is located. The layout of arrays is applied by the patient at home and maintained using a schematic illustration provided by the treating physician. Patients have used TTFields at home for at least 18 h per day and no serious systemic toxicities have been reported to be associated with the treatment [18–22]. TTFields were successfully tested in patients with newly diagnosed glioblastoma, leading to a significant prolongation of overall survival (OS) when given in combination with maintenance temozolomide [18].

The anti-mitotic effects of TTFields have been shown in multiple tumor models [17,23]. In ovarian cancer, TTFields were demonstrated to cause a maximal anti-proliferative effect at 200 kHz in multiple ovarian carcinoma cell lines [23]. Combining TTFields with paclitaxel further enhanced the apoptosis-mediated anti-mitotic effect in all tested cell lines, extending beyond the combination index threshold for synergy in some cases [23]. In vivo, TTFields in combination with paclitaxel demonstrated efficacy in a syngeneic ovarian cancer mice model. Further, simulations on a realistic human computational model demonstrated effective distribution of TTFields in the abdomen in patients with varying anatomical features [23]. These simulations, which integrate permittivity and conductivity data of the different tissues into an MRI-based phantom, allow the calculation of electric field distribution using a finite element solver.

The Phase 2 INNOVATE (EF-22) Study (NCT02244502) reported herein was the first clinical trial testing the safety and efficacy of TTFields in combination with weekly paclitaxel in patients with recurrent, platinum-resistant ovarian cancer.

2. Methods

2.1. Patients

The INNOVATE (EF-22) was a phase 2, single arm, multi-center trial testing TTFields (200 kHz) concomitant with weekly paclitaxel for recurrent ovarian cancer. The study conducted at four sites in Belgium, Switzerland and Spain enrolled a total of 31 patients between October 2014 and May 2016. The study was approved by the ethics committees of all participating centers and the relevant competent authorities, and each patient gave written informed consent prior to any study-specific procedure. The follow up period included a monthly clinical visit and a CT scan every second month, assessed by the investigator at each site. Follow up continued for at least 6 months from the enrollment of the last patient in the study. The definition of platinum-resistant ovarian cancer (PROC) per Friedlander et al. [24] is progression-free interval since last line of platinum of >1 month and <6 months.

2.2. Eligibility criteria

All patients enrolled in the trial had histologically-confirmed recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma, with any number of prior therapies. Patients were assessed to have at least 12 weeks of life expectancy and an Eastern Cooperative Oncology Group (ECOG) score of 0–1. Measurable disease according to the revised RECIST Criteria version 1.1 was required to allow radiological assessment. Adequate bone marrow, liver and renal functions were confirmed by laboratory tests prior to enrollment (absolute neutrophil count ≥1.5 $\times 10^9$/L, platelet count ≥100 $\times 10^9$/L, hemoglobin ≥10 g/dL, AST and/or ALT ≤3 × upper limit of normal range (ULN) or ≤5 × ULN if patient has documented liver metastases, bilirubin ≤1.5 × ULN, serum creatinine ≤1.5 × ULN, PT and PTT within normal limits or within therapeutic limits for patients receiving anticoagulation). Patients with untreated or symptomatic brain metastasis, as well as those with serious comorbidities, implantable electronic medical devices or history of hypersensitiveness to study treatments were excluded. Patients were not allowed to receive concurrent anti-tumor therapy beyond the study treatment.

2.3. Treatment plan

2.3.1. TTFields

The NovoTTF-100 L(O) System (Novocure, IL) (Fig. 1) is a portable, home-use medical device powered by a battery for the continuous application of TTFields to the abdomen and pelvis. The device was preprogrammed to deliver 200 kHz TTFields to the peritoneum in two sequential, perpendicular field directions at a maximal intensity of 1414 mA RMS through two pairs of transducer arrays, which were connected to the electric field generator. No adjustments to the device were performed by patients. Patients were advised to use the device for at least 18 h per day on average, with breaks in treatment allowed for personal needs (e.g. showering). Patients were instructed to use the device for a minimum of 4 weeks from treatment initiation. Application of the non-invasive transducer arrays were adjusted and approved by the study investigator for each individual patient prior to treatment start, based on the anatomical location of the tumor. Patients were advised to treat the expected skin toxicity with high potency topical steroids and to maintain good skin hygiene. Compliance with TTFields treatment was calculated based on the downloadable log file of the device.

2.3.2. Concomitant chemotherapy

All patients received weekly paclitaxel at a starting dose level of 80 mg/m^2. Paclitaxel was administered via intravenous infusion over 1 h weekly for 8 weeks and then for all subsequent cycles on days 1, 8, 15 of each subsequent 28-day cycle. Hematologic toxicities were assessed prior to each paclitaxel dose with a complete blood count (CBC) including differential and platelet count. In the event of paclitaxel toxicities, dose interruptions and modifications were employed according to the standard of care [25]. Dose re-escalation was not permitted. Any patient who continued to experience significant toxicity despite two dose level reductions of paclitaxel (70 and 60 mg/m^2) was instructed to discontinue treatment with paclitaxel but could continue TTFields therapy.

Both treatments were administered until radiological disease progression (per RECIST Criteria version 1.1), clinical disease progression or unacceptable side effects to patient, and either of them could be continued even if the other discontinued (e.g. due to toxicity).

2.4. Statistical analysis

The primary endpoint in this study was severity and frequency of treatment-related adverse event following the administration of TTFields in combination with weekly paclitaxel. The sample size was based on the assumption that weekly paclitaxel alone will lead to a grade 3 or higher toxicity in approximately 62% of patients, calculated as a median objective performance criterion (OPC) based from paclitaxel-treated historical controls [26–30]. An absolute increase of 10% in incidence of grade 3 or higher toxicity was chosen as the upper bound allowed for the combination of TTFields with weekly paclitaxel. A sample size of 30 patients could provide a one-sided 95% upper confidence limit of 10%. Acute toxicity during the treatment based on incidence and severity of treatment emergent adverse events was evaluated using the CTCAE version 4.0 in all patients starting therapy. Since skin irritation in the recurrent glioblastoma phase III study [20] was reported in 16% of patients, this percentage was used as the threshold for skin toxicity evaluation in the current trial. Thus, if <6 out of 30 patients in the study permanently discontinued TTFields due to skin toxicity beneath the arrays, the safety profile of the combination of TTFields with weekly paclitaxel at 80 mg/m^2 would be considered acceptable.

Secondary efficacy endpoints were progression free survival (PFS), which was evaluated using investigator assessment of CT images on the intent-to-treat (ITT) population. Overall survival was measured as time from trial enrollment to the date-of-death, or censored at the last follow up. PFS and OS were estimated using the Kaplan-Meier (KM)

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