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A comprehensive analysis of gestational trophoblastic neoplasia trials posted at online clinical trial registries

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ABSTRACT

Objective: We conducted a comprehensive analysis of gestational trophoblastic neoplasia (GTN) trials posted at online registries and aimed to provide useful information for future GTN trial designs.
Study design: We searched ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Portal (ICTRP) Search Portal, Australian New Zealand Clinical Trial Registry, ISRCTN Register, and Chinese Clinical Trial Register for all the clinical trials reporting GTN treatments. The general information of each trial was extracted.
Results: Twenty trials meeting the inclusion criteria were included in the final analysis. In total, 6 trials were phase II trials, 2 were phase II/III trials, 7 were phase III trials, and 1 was a phase IV trial; and the phase type of 4 trials were not reported. The conditions included low-risk GTN (n = 15), high-risk GTN (n = 2), and mixed GTN (n = 3). Randomization was performed in 15 trials, and the remaining 5 trials were single-arm trials. The median enrollment size for randomized clinical trials (RCTs) and single-arm trials was 80 and 38, respectively. Among the RCTs, parallel assignment was used in 12 trials, crossover assignment was used in 1, and the intervention models of 2 were not reported. For masking, 15 trials were open-label, 2 were single-blinded, 2 were double-blinded, and the masking status of 1 was not reported. Ovarian functions and pregnancy outcome after chemotherapy were evaluated in only 2 trials. Regarding sponsorship, 2 trials had industry sponsorship.
Conclusion: Conducting RCTs for GTN is challenging, and international collaboration and smarter clinical trial designs are required for future GTN trials.

Introduction

Gestational trophoblastic neoplasia (GTN) refers to a malignant disorder of invasive mole, choriocarcinoma, placental-site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) [1]. In clinical practice, GTN is divided into low-risk and high-risk subgroups based on the International Federation of Gynecology and Obstetrics (FIGO) 2000 systems, which was developed from the World Health Organization (WHO) scoring system [2,3]. A score of six or less indicates a low risk of developing resistance to single-agent chemotherapy, while a score greater than 6 indicates a high risk of resistance to single agent chemotherapy and therefore intially requires combination chemotherapy. Low-risk GTN (LRGTN) is often cured with either methotrexate (MTX), with or without folinic acid rescue, or actinomycin D (Act-D) [4]. Currently, several dosing/cycling options for either MTX or Act-D were developed for the treatment of LRGTN [4,5]. However, the differences in dosing/cycling options for either MTX or Act-D, and in inclusion criteria among trials make determining the superior regimen problematic [4,5]. For patients with high-risk GTN (HRGTN), etoposide, MTX, and Act-D, alternating weekly with cyclophosphamide and vincristine (EMA/CO) is the preferred first-line combination regimen [6,7]. In parts of China, however, patients with HRGTN received floxuridine, Act-D, etoposide and vincristine (FAEV) as the primary treatment [8,9]. There is no head-to-head evidence to compare the efficacy and toxicity of EMA/CO with those of FAEV. In fact, conducting clinical trials in this field is a challenge. GTN clinical trial designs are often comprised by the limited number of patients, the paucity of physicians qualified to care for them, and the poor understanding of GTN's natural history [10,11]. Conducting a GTN

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trial should be considered a precious opportunity to obtain valuable information.

In this study, we report a retrospective analysis of the past and current GTN clinical trials posted at online clinical trial registries, with the goal of provide useful information to meet the challenge of effective designs and implementations of prospective clinical trials dealing with the treatment of GTN.

Materials and methods

Trials selection

We searched ClinicalTrials.gov (www.clinicaltrials.gov), the EU Clinical Trials Register (www.clinicaltrialsregister.eu/), the WHO ICTRP Search Portal (www.who.int/ictrp/network/en/index.html), the ISRCTN Register (www.isrctn.com), the Australian New Zealand Clinical Trial Registry (www.anzctr.org.au/), and the Chinese Clinical Trial Register (www.chictr.org.cn) for all the clinical trials reporting GTN treatments using the following keywords: "gestational trophoblastic disease" or "gestational trophoblastic neoplasia" or "gestational trophoblastic tumor".

Eligibility criteria

Trials dealing with the treatment of GTN were eligible. All registered trials were scrutinized to avoid the inclusion of duplicate data. Terminated trials and observational studies were excluded.

Data acquisition

For each trial, we extracted the trial identifier, trial status, condition or disease, study design, sponsor type, years of estimated/actual study start date, and years of estimated/actual primary completion.

Statistical analysis

Data were summarized using descriptive statistics, and qualitative data were represented as frequency and percentage. Statistical analyses were performed using R version 3.3.2.

Results

Trial selection

We initially retrieved 185 trials from six online registries and excluded 165 that did not meet the inclusion criteria. Among the 165 trials, 141 were not related to the treatment of GTN, 15 were duplication studies, 2 were terminated, and 7 were observational studies. Thus, 20 trials were included in the final analysis. A flowchart of the trial selection process is depicted in Fig. 1.

Trial characteristics

The characteristics of each trial are shown in Tables 1 and 2. In total, 6 trials (30%) were phase II trials, 2 (10%) were phase II/III trials, 7 (35%) were phase III trials, and 1 (5.0%) was a phase IV trial, and the remaining 4 (20%) were not reported. The recruitment status were "not yet recruiting", "recruiting", "active, not recruiting", "completed", and "unknown" in 2 (10%), 6 (30%), 2 (10%), 9 (45%), and 1 (5%) trials, respectively. The conditions included low-risk GTN (n = 15; n = 75%), high-risk GTN (n = 2; 10%), and mixed GTN (n = 3; 15%). Randomization was performed in 15 trials (75%), and the remaining 5 (25%) were single-arm trials. The median

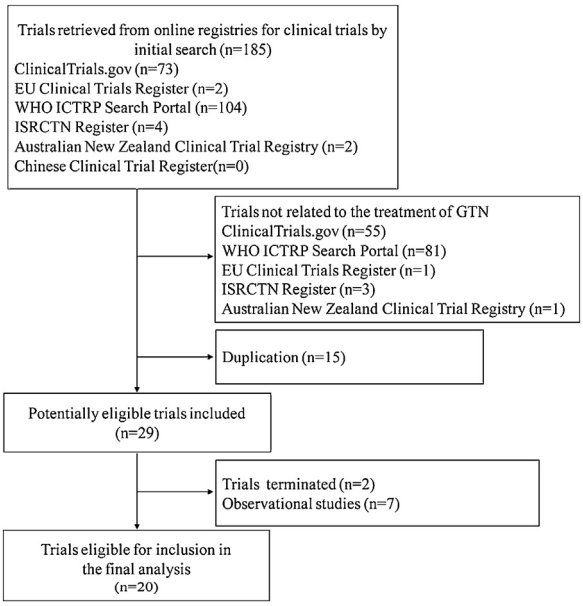

Fig. 1. The flowchart of the trial selection process.

enrollment size for RCTs was 80 (Q1 = 52.75, Q3 = 203), and the median enrollment size for single-arm trials was 38 (Q1 = 32, Q3 = 50). Among the RCTs, parallel assignment was employed in 12 trials (80%), crossover assignment was employed in 1 (6.7%), and the intervention models of the remaining 2 (12.3%) were not reported. For masking, 15 trials (75%) were open-label, 2 (10%) were single-blinded, 2 (10%) were double-blinded, and the masking status of the remaining one was not reported. Ovarian functions and pregnancy outcomes after chemotherapy were evaluated in only 2 trials (10%). Two trials (10%) had industry sponsorship.

Discussion

GTN is a rare and highly chemosensitive group of diseases. However, it remains unclear which chemotherapy regimens are the most effective and the least toxic first-line treatments [4,12,13]. Moreover, 25% of patients with GTN will develop recurrence of or resistance to initial chemotherapy [12]. These patients must resort to salvage chemotherapy with or without surgery. There is also no confirmed evidence to determine the efficacy and safety of the salvage chemotherapy for managing GTN [12,14–16]. In fact, conducting RCTs, which are considered the gold standard for assessing the efficacy and safety of clinical interventions, is challenging in this field due to a limited number of patients, the paucity of physicians qualified to care for them, and the poor understanding of GTN's natural history. A comprehensive analysis of the past and current clinical GTN trials would facilitate the conduct of prospective clinical trials dealing with the treatment of GTN.

Phase II trials play important roles in identifying treatment regimens with the highest probability of succeeding in subsequent phase III trials [17,18]. Our results indicate that both single-arm and randomized phase II GTN trials have been successfully conducted. However, most phase II GTN trials are single-arm trials. This is unsurprising since GTN is a rare disease, and single-arm trials usually involve smaller sample sizes, requiring less time to complete and fewer resources invested. However, single-arm phase II trials are limited by two classic epidemiological factors, selection bias and confounding [17]. The results of single-