Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The efficacy and safety of first-line single-agent chemotherapy regimens in low-risk gestational trophoblastic neoplasia: A network meta-analysis

Jun Li [a,b], Shufen Li [c], Hinlin Yu [a,b], Jieyu Wang [a,b], Congjian Xu [a,b], Xin Lu [a,b,*]

[a] Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China
[b] Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai, China
[c] State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Er Rd., Shanghai, China

HIGHLIGHTS

- 5d-IV Act-D and pulsed IV Act-D appear to be the best treatment options in LRGTN.
- Pulsed Act-D is the least toxic in nausea and vomiting.
- Grade 3/4 AEs are more frequently observed in 5d-IM MTX, followed by 5d-IV Act-D.

ARTICLE INFO

Article history:
Received 10 September 2017
Received in revised form 18 November 2017
Accepted 24 November 2017
Available online xxxx

Keywords:
Gestational trophoblastic neoplasia
Low risk
Chemotherapy
Network meta-analysis

ABSTRACT

Objective. There is no consensus regarding what should be the optimal single-agent regimen in low-risk gestational trophoblastic neoplasia(LRGTN). we performed this network meta-analysis(NMA) and our aim is to synthesize all efficacy evidence, enabling a comparison of all single-agent methotrexate(MTX)-based or actinomycin-d(Act-D)-based regimens in LRGTN.

Methods. We performed a literature search of PubMed, Embase, and the Cochrane Library for all relevant articles. Seven randomized controlled trials and four retrospective studies met the study eligibility criteria. Overall, 987 patients were included. Treatments were grouped into weekly intramuscular MTX(w-IM MTX), five-day intramuscular MTX(5d-IM MTX), five-day intravenous MTX(5d-IV MTX), eight-day intramuscular MTX with folinic acid(MTX-FA), five-day intravenous Act-D(5d-IV Act-D), and bi-weekly pulsed intravenous Act-D (pulsed IV Act-D) treatments. P-score was used to rank the treatments.

Results. Values of P-score indicated that the Act-D-based regimens had superior efficacy compared with the MTX-based regimens. Namely, 5d-IV Act-D had the highest probability of being the best treatment arm for CR, followed by pulsed IV Act-D and 5d-IV MTX. Similar results were observed in the subgroup analysis from the prospective studies. Toxicity analysis indicated that 5d-IM MTX showed increased toxicity in nausea and vomiting, as measured by their P-scores. In contrast, 5d-IV Act-D had the highest probability of being the least toxic regimen in terms of nausea and vomiting. Grade 3/4 adverse events (AEs), though infrequent, were more frequently observed in 5d-IM MTX, followed by 5d-IV Act-D and 5d-IV MTX.

Conclusions. Our NMA provides a systematic evaluation of the relative efficacy of available single-agent MTX-based and Act-D-based regimes in LRGTN. Until new evidence becomes available, 5d-IV Act-D and pulsed IV Act-D appear to be the best treatment options in LRGTN.

1. Introduction

Gestational trophoblastic neoplasia (GTN) refers to a group of diseases mainly including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor [1]. According to the modified International Federation of Gynecology and Obstetrics/World Health Organization (FIGO/WHO) scoring system, low-risk GTN (LRGTN) is defined by a FIGO stage I-III with a WHO score of six or below [2–4]. It is a rare but highly curable disease. Many effective chemotherapy regimens are used worldwide for the treatment of LRGTN. In 1956, methotrexate(MTX) was first reported to be successful in the treatment of GTN [5]. Since then, several dosing/cycling options for MTX have been developed for the treatment of LRGTN, including but not limited to weekly intramuscular MTX (w-IM MTX), five-day

* Corresponding author at: Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, No. 419, Fangxie Road, Shanghai 200011, China.
E-mail address: 052108365@fudan.edu.cn (X. Lu).

https://doi.org/10.1016/j.ygyno.2017.11.031
0090-8258/

intramuscular MTX (5d-IM MTX), five-day intravenous MTX (5d-IV MTX), and eight-day intramuscular MTX with folinic acid (MTX-FA) [6]. Single-agent actinomycin-d (Act-D) was initially introduced as an effective salvage regimen in MTX-resistant LRGTN patients in 1962 [7]. By 1972, Act-D had been reported as an alternative drug for initial therapy [8]. Recently, two main Act-D-based regimens, including five-day intravenous Act-D (5d-IV Act-D) and bi-weekly pulsed intravenous Act-D (pulsed IV Act-D), have been developed and reported to be as effective as MTX-based regimens in the treatment of LRGTN [6,9]. However, direct comparisons of these different regimens are lacking, which makes it extremely difficult to evaluate the comparable benefits and risks of each regimen. Thus, we performed this network meta-analysis (NMA) and our aim is to synthesize all efficacy evidence, enabling a comparison of all single-agent MTX-based or Act-D-based regimens for LRGTN.

2. Methods

2.1. Search strategy

Searches were performed in PubMed, Embase, and the Cochrane Library for all relevant articles with the following search algorithm: gestational trophoblastic disease OR gestational trophoblastic neoplasia OR gestational trophoblastic tumor OR gestational trophoblastic neoplasm OR invasive mole OR choriocarcinoma OR GTD OR GTN OR GTT, chemotherapy, low risk. The last search was updated on July 11, 2017. In addition, the reference lists of all studies met the eligibility criteria, and critical reviews were also examined for other potentially relevant articles missed by initial searches.

2.2. Eligibility criteria

Inclusion and exclusion criteria were prespecified. The eligibility criteria were as follows. (i) The studies that compared an MTX regimen directly to an Act-D regimen for treatment of LRGTN were considered. (ii) The definition of LRGTN was based on the earlier FIGO/WHO 2000 scoring system or the modified WHO scoring system. A risk score of 6 and below is classified as low risk. (iii) The studies should provide information about the characteristics of patients and if they were matched for potentially confounding variables in each treatment group. (iv) If the patient populations overlapped between studies, only the most recent and informative publication was included.

2.3. Data extraction

Data was extracted independently by two authors (Jun Li and Shufen Li), and discrepancies were adjudicated by Professor Xin Lu. For each eligible study, the first author, year of publication, country of origin, sample size, treatment regimens, and classification system of LRGTN were recorded. The interesting outcomes, including complete response (CR) rate and selected toxicities, were also recorded.

2.4. Statistical analysis

Pair-wise meta-analyses were performed using Stata 11.0 software. The NMA was performed using a frequentist approach and the R package netmeta [10]. P-score was used to rank the treatments. Fixed- or random-effects frequentist network meta-analysis models were applied where appropriate.

3. Results

3.1. Identification of eligible studies

The review flow is depicted in Fig. 1. A total of 736 studies were identified after initial search. After removing duplicates, 472 records were reviewed on title and abstract; 452 records were excluded from further analysis. Then, the remaining 20 articles were assessed for eligibility. After full-text evaluation, 10 out of these 20 studies were included. In addition, one study published in Persian was added to our list after manually checking the reference lists of the published Cochrane Library reviews. In total, seven randomized clinical trials (RCTs) and four retrospective studies were included in our NMA [11–21]. There are six first-line, single-agent treatment regimens: (1) w-IM MTX, (2) 5d-IM

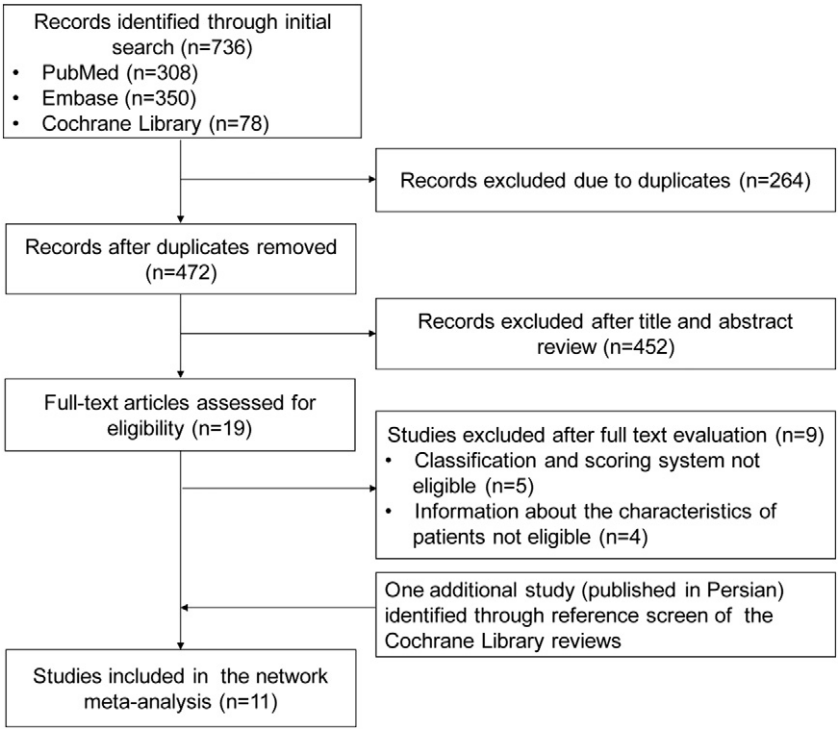

Fig. 1. PRISMA flowchart of the literature search for LRGTN.

Please cite this article as: J. Li, et al., The efficacy and safety of first-line single-agent chemotherapy regimens in low-risk gestational trophoblastic neoplasia: A networ..., Gynecol Oncol (2017), https://doi.org/10.1016/j.ygyno.2017.11.031