



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Editorial

The first-line therapy for low-risk gestational trophoblastic neoplasia: Does single agent or multi-agent work?

In this May issue of the *Taiwanese Journal of the Obstetrics and Gynecology*, we are glad to comment the publication by Dr. Zhu and colleagues on their topic of low-risk gestational trophoblastic neoplasia outcome after treatment with VMP regimen from 2005 to 2017 [1]. The authors retrospectively reviewed 68 patients with low-risk gestational trophoblastic neoplasia (GTN), according to the International Federation of Gynecology and Obstetrics (FIGO 2000) staging system, treated by multi-agent chemotherapy of VMP regimen, including vincristine (2.0 mg, intravenous route, day 1), methotrexate (0.4 mg/kg, intramuscular route, day 1,2,3,4,5), and platinum (cisplatin [75 mg/m², intravenous route for 3 days], carboplatin or nedaplatin) and found that 57 patients (83.8%) achieve complete remission [1], compared with 63.6% (42/66) of complete remission rate of the similar patients treated with single agent of methotrexate (0.4 mg/kg, intramuscular route, day 1,2,3,4,5) [1]. The efficacy of their VMP treatment (5-day VMP regimen) was higher than that of methotrexate (63.6%) or actinomycin-D single agent chemotherapy claimed by authors [1], contributing to their conclusion that for patients diagnosed with low-risk GTN, VMP regimen was a safe and effective treatment with a high rate of remission. The current study is interesting and worthy of further discussion.

First, before discussing the GTN, the accurate diagnosis of GTN is important, since there are at least five main clinico-pathological forms available, including hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor [2–6]. The treatment of choice of each-type GTN depends on the clinic-pathological diagnosis and FIGO score [7]. For example, mole and invasive mole are often treated with suction curettage; placental site trophoblastic tumor and epithelioid trophoblastic tumor were candidate of surgical approach; by contrast, choriocarcinoma needs chemotherapy.

Second, Bolze's formalized consensus of the European Organization for Treatment of Trophoblastic Diseases in 2015 suggested the followings [7], which can be used to comment Dr. Zhu's article [1], including (1) single agent chemotherapy is the recommended treatment for low-risk GTN with a overall cure rate close to 100% and (2) methotrexate (MTX) is the recommended first line single agent treatment of low-risk GTN [7]. In addition, a recent Cochrane review in 2016 reported that actinomycin D is probably more likely to achieve a primary cure in women with low-risk GTN, and less likely to result in treatment failure, than a methotrexate regimen, although actinomycin D may be associated with a greater risk of severe adverse events than a methotrexate regimen, and concluded that the direction of effect still favors methotrexate, although more evidence is needed [8]. In fact, it is well known that low-risk GTN is recommended to be treated with single agent

chemotherapy but may require additional agents, and most of importance, although some (near one-fourth) are associated with more drug resistance, overall survival still approaches 100% [9]. Furthermore, many studies used the other single agent, such as actinomycin D or etoposide as the second-line protocol in the management of patients low-risk GTN after failed first-line methotrexate treatment, and the complete response rate after second-line therapy achieves 75% [10]. More over, the use of multiagent chemotherapy has a higher risk of deterioration of reproductive outcome in women with GTN than that of single agent chemotherapy [11]. MITO-9 study found temporary amenorrhea occurred in 33% of the single agent chemotherapy group and 66.7% of the multiagent chemotherapy group and of most importance, premature ovarian menopause only occurred in the multiagent chemotherapy group (up to 9%) [11]. Finally, a recent network meta-analysis concluded that 5-day intravenous actinomycin-D and pulsed intravenous actinomycin-D appear to be the best treatment opinions in low-risk GTN until new evidence becomes available [12]. All favored that single-agent chemotherapy is still a better choice as the first-line therapy for low-risk GTN.

Third, even though the use of single-agent chemotherapy in the management of low-risk GTN is well accepted, different drugs or different administration protocol still influences the therapeutic outcome [13,14]. For example, one study from the New England Trophoblastic Disease Center showed 8-day methotrexate/folinic acid remains the treatment of choice at low-risk GTN compared to one-day methotrexate infusion protocol [15]. All suggested that the argument about the management of GTN is still present and we favor much more interests obtained from the audience to study this unusual disease-GTN.

Conflicts of interest

All authors declare no conflict of interest.

Acknowledgements

Supported by grants from the Ministry of Science and Technology, Executive Yuan (MOST 106-2314-B-075-061-MY3), and Taipei Veterans General Hospital (V108C-085).

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