Systematic Review

EMA and EMACO Chemotherapy in High Risk Gestational Trophoblast Disease, which Better?

Kemoterapi EMA dan EMACO dalam Risiko Tinggi Penyakit Trofoblas Gestasional, Mana yang Lebih Baik?

[1]I Gde S. Winata, [1]Putra A. E. Aricandana

[1]Departement of Obstetrics and Gynecology, Faculty of Medicine Udayana University/Sanglah Central General Hospital, Denpasar

Abstract

Objective: Determine the best effectiveness and efficacy between EMA and EMACO for patients with high-risk GTN.

Results: GTN patients who received EMA showed remissions as high as 74.4% - 96.6% of cases. The side effects of anemia in EMA were less toxic than EMACO, but it wasn't the case in neutropenia. Two studies showed that 57,1% and 87% patients relapse within 2 years, while none in 5 years and 7 years follow-ups.

Discussion: With EMACO use, it has been observed to result in increased morbidity and increased health care costs and when patients experience complications while staying overnight in the hospital, they are not monitored by a good specialist team. Patients treated with EMACO had more peripheral neuropathy as result of vincristine than EMA. The use of EMA certainly requires further evaluation.

Conclusion: Patients with High-risk GTN who treated first-line with EMA or EMACO have an excellent prognosis. Both regiments are equally effective. There were differences in treatment scheduling, hospitalization requirements, and toxicity between regimens.

Keywords: EMA, EMACO, gestational trophoblastic neoplasia.

Abstrak

Tujuan: *Mengetahui efektivitas dan efikasi terbaik diantara EMA dan EMACO untuk pasien dengan NTG berisiko tinggi.*

Hasil: *Pasien dengan NTG yang menerima EMA menunjukkan remisi setinggi 74.4%-96.6% dari kasus. Efek samping anemia dari EMA lebih tidak toksik dibandingkan EMACO, namun tidak dengan neutropenia. Dua studi menunjukkan bahwa 57.1% dan 87% pasien mengalami kekambuhan dalam 2 tahun, namun tidak ada dalam follow up 5 tahun dan 7 tahun.*

Diskusi: *Dengan penggunaan EMACO, dapat diobservasi bahwa terdapat peningkatan morbiditas dan peningkatan biaya pelayanan kesehatan, dan ketika pasien mengalami komplikasi pada saat rawat inap di rumah sakit, mereka tidak dimonitor oleh tim spesialis yang baik. Pasien yang diterapi dengan EMACO memiliki efek samping neuropati perifer lebih tinggi yang disebabkan oleh vinkristin, dibandingkan EMA. Penggunaan EMA membutuhkan evaluasi lebih lanjut.*

Kesimpulan: *Pasien dengan NTG berisiko tinggi yang diterapi dengan lini pertama EMA atau EMACO mempunya prognosis yang baik. Kedua regimen tersebut efektif. Ada perbedaan dalam penjadwalan terapi, kebutuhan rawat inap dan toksisitas antara regimen.*

Kata kunci: *EMA, EMACO, neoplasia trofoblastik gestasional.*

Correspondence author. I Gde S. Winata. Departement of Obstetrics and Gynecology, Faculty of Medicine Udayana University/Sanglah Central General Hospital, Denpasar. Email: dedekcakantara@gmail.com

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INTRODUCTION

Gestational Trophoblast Neoplasia (GTN) is a malignant form of Gestational Trophoblast Disease (GTD). GTN refers to a spectrum of diseases mainly including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN is a rare disease. Estimated incidence is 1 case per 40,000 pregnancies. This condition usually occurs after a previous pregnancy with a history of miscarriage and an ectopic or molar pregnancy.[1]

Guidelines from the International Federation of Gynecology and Obstetrics (FIGO) are used to guide treatment decisions.[2] Patients with a FIGO score ≤ 6 should be treated with single agent chemotherapy. Furthermore, a FIGO score ≥ 7 indicates a high risk of resistance to single agent chemotherapy and this also requires multi-agent chemotherapy. However, if a FIGO score ≥

12 indicates a high risk of treatment failure and a poor prognosis.[2] GTN is highly curable with chemotherapy even with extensive metastases.[2] With proper treatment, survival rates are as high as 90-100%.[2] Previous research report better survival rates for high-risk patients which seen in patients treated with multiagent regimens as much as 65-70% compared to single agent regimen is 14-39%.[3] For this reason, multiagent regimens are recommended as first-line treatment in high-risk GTN.[4]

RESULT

Evidence of efficacy and tolerable toxicity suggests EMACO (etoposide, methotrexate, actinomycin-D with cyclophosphamide and oncovin/vincristine) is the most widely used multiagent regimen for GTN. Previous studies reported that GTN patients who received EMA showed remissions 74.4 to 96.6% of cases. Previous data suggest the side effects of anemia in EMA are less toxic than EMACO, but not for neutropenia.5 Four other studies also report comparable remission rates in patients receiving EMA: 89.7% (United States), 74.4% (Japan), 75.5% (UK), and 96% (South Korea).[5] EMA and EMACO have comparable remission rates as the first-line multiagent regimen in GTN.[7]

Treatment variables and outcomes with EMA vs EMACO.[4]

Variables and outcomes	EMA (n = 44)	EMACO (n = 39)	*P-value*
Variables			
Time to start chemotherapy (days)	4(0.8)	6 (0.12)	0.388
Proportion of delayed CMT cycles/ total cycles	18/151(11.9)	12/208 (6.4)	0.059
Adjuvant surgery (yes/no)	4(9.1)	8 (20.5)	
Hysterectomy	2	7	0.211
Lobectomy	1	1	
Craniotomy	1	0	
Embolization	0	1	
Tumor debulking	0	3	
Outcomes			
Complete remission rates	43 (97.7)	28 (71.8)	
Median time to complete remission (weeks)	12 (95% CI, 10.53-13.47)	13.1 (95% CI, 9.31-16.98)	0.001
Number of CMT (cycles)	3 (2.5)	5 (4.7)	
Relapse rate	1/43 (2.3)	6/28 (21.4)	<0.001
Time to relapse (months)	29.9	6.2 (3.1,27.1)	0.013
0-6	0	3	
>6-12	0	1	
>12-24	0	0	
>24-60	1	2	
Death rate	1 (2.3)	2 (5.1)	
Disease-related death	0	2	
Non-disease-related death	1	0	0.599
Subsequent pregnancy (pregnancies)	5	6	
Abortion	2	1	
Normal pregnancy	3	5	

Data are n(%) or median (p25, p75).
E=etoposide; M=methotrexate; A=actinomycin-D; C=cyclophosphamide; O=vincristine; CMT=chemotherapy.
Bold values were considered statistically significant at p-values <0.05

This study report that time required to complete remission between the two groups was similar. This raises the logical question whether the EMA can be considered as an alternative to EMACO. Theoretically, EMA is simpler and cheaper way. However, it does vary depending on the local payment environment and practice patterns. In addition, EMA does not use cyclophosphamide which associated with gonadotoxicity and premature ovarian failure.[6] This study also show the long-term outcome relapse in patients receiving EMACO was greater than EMA. Total of 7 patients who relapse, 4 patients (57.1%) relapse within 2 years. Furthermore, there was no relapse after 5 years of follow-up. This data relates to recent study which show 87% GTN patients

relapse within 2 years and subsequently had no relapse after 7 years.[7] This study conclude that EMA and EMACO had same remission rates and time to complete treatment. EMA is associated with a high incidence of neutropenia and its toxicity can be minimized with routinely use of CGSF (colony-granulocyte stimulating factors). In order to directly compare the efficacy between EMA and EMACO, it is important to compare outcomes in contemporary groups, even in non-randomized observational study settings.[4]

DISCUSSION

Gestational Trophoblastic Neoplasia (GTN) comprises of malignancies related to pregnancy. GTN is estimated to have an incidence of 1 case per 40,000 pregnancies, making it a rare condition. GTN, even with widespread metastasis, has a high rate of cure. Overall survival rate can be as high as 90-100% with appropriate and timely treatment.[4]

However, estimation of survival rate is misleading because the prognosis of patients with FIGO scores ≥12 is significantly worse than patients with FIGO scores <12.[2,8] Subsequent studies show the mortality rate of patients with FIGO score > 13 was significantly higher than FIGO score <13.[9] FIGO Cancer define very high risk GTN is a subgroup with a FIGO score ≥13.[2]

Health care policies are implemented to improve patient safety, quality, effectiveness, and patient satisfaction. A strong rationale reason for changing the EMACO regimen is to reduce the length of a patient's hospital stay.[10] With EMACO, it has been observed to result in increased morbidity and increased health care costs and when patients experience complications while staying overnight in the hospital, they are not monitored by a good specialist team.[10]

Patients treated with EMACO had more peripheral neuropathy as result of vincristine than EMA. Neurotoxicity in GTD patients has a negative impact on the patient's health-related quality of life (HRQoL). In a systematic review, HRQoL in GTD patients who received more intensive chemotherapy had worse quality of life outcomes including physical, social, and psychosocial functioning.[11]

The use of EMA certainly requires further evaluation. As a direct result of the COVID-19 pandemic, Singh *et al* have temporarily changed the first-line treatment protocol for high-risk GTN to 2-day EMA every 2 weeks with 5 days of 5 mcg / kg / day CGSF support and remove CO to reduce myelosuppression potential and number of hospital visits.[4,7]

CONCLUSION

Patients with high-risk GTN who treated first-line with EMA or EMACO have an excellent prognosis. EMA was associated with less toxicity and treatment delay, although with a similar duration of treatment to EMACO. Use of EMACO was associated with increased neutropenia, non-neutropenic grade 3-4 infections, peripheral neuropathy, delayed treatment, and longer non-elective nights in hospital. Both regimens are equally effective. There were differences in treatment scheduling, hospitalization requirements, and toxicity between regimens. This can be considered according to the patient's personal, social and family circumstances to optimize treatment.

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