Epidemiology, treatment patterns, and outcomes in gestational trophoblastic neoplasia: a systematic literature review and gap analysis

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CONCLUSIONS

- This systematic literature review (SLR) summarized the epidemiology, efficacy, safety, and unmet needs of patients with gestational trophoblastic neoplasia (GTN), with most evidence focused on descriptive analyses
- The incidence of GTN in patients with gestational trophoblastic disease (GTD) ranged from 6.2% (in the UK) to 19.2% (in Asia)
- General consensus was observed regarding the use of methotrexate (MTX) or dactinomycin (Act-D) as first-line (1L) treatment in patients with low-risk GTN
- Treatment regimens were more diverse in patients with high-risk GTN and in those who received later lines of treatment
- Immune checkpoint inhibitors (ICIs) were reported in recent clinical guidelines as potential options for patients with 1L treatment failure or for high-risk GTN
- 1L regimens are not interchangeable, and unmet needs persist to improve response rates and minimize toxicity
- More research is warranted to investigate the role of 1L ICI combination therapy vs the current standard of care of single-agent chemotherapy to optimize outcomes in certain patients with this rare gynecologic malignancy and support physicians in treatment decisions[1]

PLAIN LANGUAGE SUMMARY

- Gestational trophoblastic neoplasia, or GTN, is a rare cancer that can occur in tissues of the womb
- In this study, researchers looked at results from 117 different studies of women with GTN, including studies investigating different treatments
  - In women who took part in the studies, the average age for developing GTN was 33 years
- The most common first treatment for GTN was chemotherapy with drugs called dactinomycin or methotrexate
  - In clinical trials, the proportion of women with GTN who had a response to treatment was higher with dactinomycin (88%) than with methotrexate (76%)
  - However, women treated with dactinomycin were more likely to feel sick or have other stomach problems than women treated with methotrexate
  - Across different studies, 80% of women who became pregnant after finishing treatment for GTN had a successful pregnancy
- Overall, findings from this study show that further research is needed to find more effective treatments for GTN that have fewer side effects

BACKGROUND

- GTN encompasses a number of rare, malignant tumors, including invasive moles, choriocarcinoma, placental-site trophoblastic tumors, and epithelioid trophoblastic tumors[2]
- Disease severity is evaluated using the International Federation of Gynecology and Obstetrics (FIGO) anatomical stage and World Health Organization (WHO) prognostic score[3]
- Patients with FIGO stage I or stage II/III GTN and a WHO prognostic score <7 have low-risk disease and are treated with single-agent chemotherapy, typically either MTX or Act-D, whereas patients with high-risk disease may be treated with multiagent chemotherapy
- Recent and ongoing clinical trials are evaluating the efficacy of immunotherapy in the treatment of GTN[1]
- The current study aimed to understand the epidemiology, treatment patterns, and outcomes in patients with GTN in addition to unmet needs for innovative treatments

METHODS

Data source and search strategy

- This SLR examined English-language publications on GTN found in Embase and MEDLINE via Ovid (previous 20 years for interventional studies and 5 years for observational studies), plus relevant abstracts from target conferences from 2022-2024 (**Figure 1**)

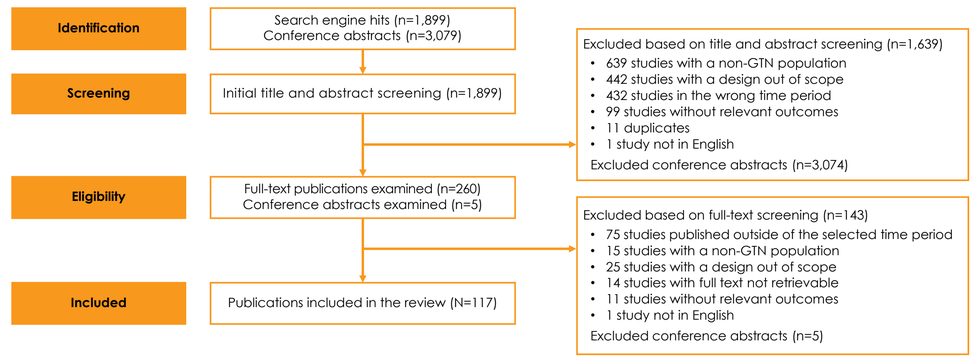
Study selection and data extraction

- 1,639 abstracts and 260 full-text studies were screened for inclusion
- Studies not in English, studies on benign GTD, and case reports and case series were excluded
- Screening and extraction were performed by 2 independent reviewers; study quality was assessed using relevant instruments

Statistical analyses

- Pooled objective response rates and 95% CIs with 1L MTX or Act-D monotherapy were calculated using random-effects models
- Descriptive statistics, including means, medians, interquartile ranges, frequencies, and percentages, were used to summarize extracted information

Figure 1. PRISMA diagram of study selection



GTN, gestational trophoblastic neoplasia; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS

Study overview

- 117 studies were included, of which two-thirds were cohort studies (n=78 [66.7%]) and approximately half (n=64 [54.7%]) were conducted in Asia (**Figure 2**)
- GTN incidence varied widely by region and setting; the incidence of GTN among all registered patients with GTD in the UK was 6.2%, whereas the incidence in 3 hospital-based studies in Asia was 19.2%

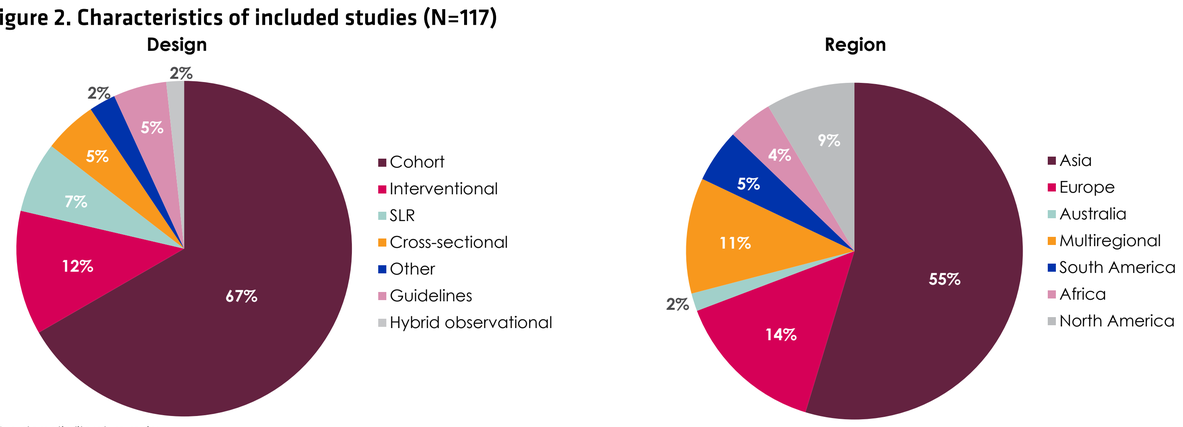
Patient characteristics

- Across 53 studies reporting continuous age data, the mean of mean ages was 33.0 years, and the range of means was 26.8-51.3 years
- In 42 studies reporting WHO prognostic scores at diagnosis, 6,346 (77.2%) of 8,225 patients were classified as having low-risk disease and 1,879 (22.8%) were classified as having high-risk disease

Treatment patterns

- 81 studies reported treatment information
- In observational studies, the most common 1L treatments for low-risk GTN were MTX (n=16) and Act-D (n=6)
- Treatments used in the second line and in patients with high-risk disease included diverse multiagent regimens and immunotherapy

Figure 2. Characteristics of included studies (N=117)



SLR, systematic literature review.

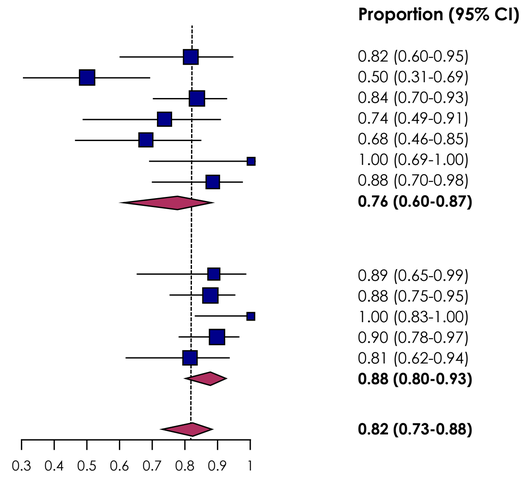
Efficacy outcomes

- Across clinical trials, the response rate with 1L treatment was higher with Act-D (87.8% [95% CI, 80.3%-92.7%]) vs MTX (76.4% [95% CI, 60.3%-87.4%]) (**Figure 3**)
- In observational studies, response rates were similar and were inversely associated with GTN risk score (**Table 1**)
- 10 observational studies reported that patients often had successful pregnancies following fertility-sparing treatment; 5 studies reported 105 successful live births from 131 pregnancies following treatment for GTN (80.2%)

Safety outcomes

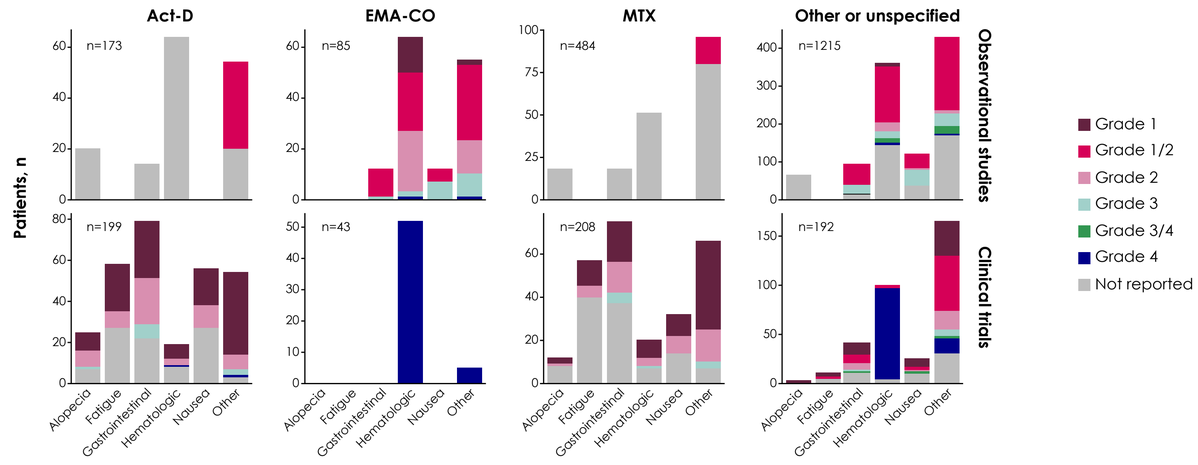
- In interventional and observational studies, the incidence of nausea and other gastrointestinal adverse events was higher with Act-D vs MTX (**Figure 4**)

Figure 3. Response rate with 1L treatment in clinical trials



1L, first line; **Act-D**, dactinomycin; **df**, degree of freedom; **MTX**, methotrexate.

Figure 4. Reported adverse events in interventional clinical trials and observational studies in GTN*



Act-D, dactinomycin; **EMA-CO**, etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine; **GTN**, gestational trophoblastic neoplasia; **MTX**, methotrexate.
*Individual patients may have reported >1 outcome per unique event group.

Table 1. Summarized clinical responses with 1L treatment reported in observational studies with specified risk

Clinical response	Drug	Risk	Studies, n	Patients at risk of given outcome, n	Patients with response, %	Patients with response in studies reporting given outcome, mean (SD), %
Any response	Act-D	Low	4	1,705	920 (53.96)	65.34 (37.3)
	Act-D	High	2	2,001	774 (38.68)	23.61 (36.32)
	MTX	Low	6	1,368	1,052 (76.9)	64.68 (36.1)
	Other	Low	6	399	295 (73.93)	74.71 (25.23)
	Other	High	9	603	354 (58.71)	58.79 (34.38)
Complete response	Act-D	Low	3	1,026	818 (79.73)	77.71 (4.4)
	Act-D	High	1	994	764 (76.86)	76.86 (NA)
	MTX	Low	3	978	705 (72.09)	79.85 (17.77)
	Other	Low	2	93	78 (83.87)	86.62 (14.65)
	Other	High	3	233	217 (93.13)	88.4 (14.27)
Recurrence	Act-D	Low	1	570	15 (2.63)	2.63 (NA)
	Act-D	High	2	1,007	28 (2.78)	5.67 (7.59)
	MTX	Low	2	190	7 (3.68)	3.56 (3.57)
	Other	High	1	87	6 (6.9)	6 (NA)

1L, first line; **Act-D**, dactinomycin; **MTX**, methotrexate; **NA**, not available.

LIMITATIONS

- This SLR was subject to standard search and selection biases, and there was a high level of study heterogeneity; study quality also varied widely
- Follow-up periods for clinical outcomes and adverse event reporting differed between studies
- Data not related to clinical response are summarized qualitatively; because of the heterogeneity of reported outcomes and populations evaluated, meta-analysis only quantified objective response rates for MTX and Act-D, and no additional statistical comparisons were conducted
- Generalizability of individual study results is dependent on the design and selection criteria used; some studies reported national-level results and others reported single-institution data
- This SLR was global in nature and broad in scope but included studies published in English only

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REFERENCES 1. Wang W, et al. Gynecol Obstet Clin Med. 2025;5(1):e000194. **2.** Horowitz NS, et al. Gynecol Oncol. 2021;163(3):605-13. **3.** Jin-Kai L, et al. EClinicalMedicine. 2024;77:102890. **DISCLOSURES M. Kearney** reports employment with Merck and stock or other ownership interests with Merck, Novartis, and UCB. **J. Hoffman** reports employment with EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, and stock or other ownership interests with Merck, MSD, and Pfizer. **L. Cilek** reports employment with GIPAM GmbH, Wismar, Germany, which received funding from Merck in association with this study. **J. Simeone** reports employment with GIPAM Inc., Winchester, MA, USA, and stock or other ownership interests with GIPAM GmbH, which received funding from Merck in association with this study. **ACKNOWLEDGMENTS** This study was funded by Merck (CrossRef Funder ID: 10.13039/100009945). Editorial support was provided by Nucleus Global and was funded by Merck.

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