Southern African Journal of Gynaecological Oncology 2019; 11(1):21-24

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

GUIDELINES

Managing gestational trophoblastic neoplasm (GTN) and people living with HIV (PLWH)

P Barnardt

Department of Imaging and Clinical Oncology, Stellenbosch University, South Africa
Corresponding author, email: pieterb@sun.ac.za

The 2017 World Health Organization (WHO) global report on HIV/AIDS estimated that sub-Saharan Africa comprised 64% of the global HIV burden, with a current estimate of 19.4 million cases in Eastern and Southern Africa. Since the introduction of antiretroviral therapy (ART) there has been a 30–40% increase in the incidence of non-AIDS malignancies. Gestational trophoblastic disease comprises of a spectrum of pregnancy-related disorders with an overall cure rate of 90%. The response to treatment is generally favourable but the associated complications of HIV, comorbidities, poor performance status and extent of metastatic disease in gestational trophoblastic neoplasm patients receiving chemotherapy, compromises the outcome and survival.

Keywords: Gestational trophoblastic neoplasm, HIV, People living with HIV

Introduction

Gestational trophoblastic disease (GTD) consists of a spectrum of disorders that range from premalignant molar pregnancies to malignant tumours. Gestational trophoblastic neoplasm (GTN) is the result of a malignant transformation of placental villous and extravillous trophoblasts and it is important to remember that these lesions arise from foetal and not maternal tissue. After evacuation, trophoblastic tissue can persist in 20% of patients. GTN can arise from a normal or abnormal pregnancy and includes persistent or invasive mole (75%), choriocarcinoma (25%) and the rare placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The WHO-classification also includes an unclassified trophoblastic tumour category.[1-6]

The incidence of GTN differs amongst countries around the world with reported high incidence in South-East Asia of 15–19/1000 births, while a low incidence is observed in the Western World with 0.12–0.7/1000 births. Risk factors for GTN include a prior molar pregnancy, advance maternal age (> 40yrs), Asian and American-Indian ancestry, theca lutein cysts larger than 6 cm, excessive uterine growth, and a pre-evacuation human chorionic gonadotropin (hCG) level of more than 100 000 IU/L. GTN have an excellent prognosis with prompt diagnosis and appropriate therapy.[2,3,6]

Although human immunodeficiency virus (HIV) is not an apparent risk factor for GTN, HIV patients tend to present with advanced GTN disease, and have a significantly worse prognosis. Globally 51% of people living with HIV (PLWH) are female and AIDS-related illnesses are still the leading cause of death among women of reproductive age between 15–49 years. Sub-Saharan Africa represents 64% of the global HIV-burden and Eastern and Southern Africa reported an estimated 19.4 million cases. Globally, 17% of the world population is currently living with HIV/AIDS with 750 000 newly infected adults and children, and 420 000 deaths due to AIDS related disease. In 2016, for the first time, deaths from AIDS-related illnesses declined 27% among women and young girls according to the 2017 UNAIDS Data report.[7]

Since the introduction of antiretroviral therapy (ART) an increase in non-AIDS (NAIDS) malignancies is observed with an incidence of 30–40% among PLWH, and since 2010, NAIDS malignancy has outnumbered AIDS-defining cancers. Factors that contribute to NAIDS malignancy include the lack of autoimmune surveillance, the imbalance that exists between cellular differentiation and proliferation, and the repeated antigen stimulation that lead to proliferation of abnormal cells. Patients present at a younger age with atypical presentations, and metastatic disease that is more aggressive in behavior.[8,9]

PLWH live longer due to antiretroviral therapy (ART) and develop cancers relating to HIV and ageing. The disparity in cancer care is large and significant, and PLWH are 2–3 times more likely to receive no cancer treatment compared to uninfected people. This might be due to a lack of management guidelines, the potential for drug interactions, overlapping toxicities between cancer drugs and ART that might further enhance immunosuppression, with an increased risk of infectious compilations. In PLWH, routine screening is less frequent than in the general population. Clinicians should be vigilant to symptoms suggestive of early malignant disease and help patients to minimize risk factors for cancer: smoking cessation programs, HPV vaccines, HBV vaccine and the treatment of hepatitis B and hepatitis C infection. PLWH are generally poor surgical candidates with an increased risk of postoperative infections.[10] More PLWH and cancer should receive appropriate cancer treatment.

PLWH also experience a higher cancer-specific mortality independent of cancer stage or cancer treatment and immunosuppression may play a role in the increased cancer-specific mortality that supports the rationale for early initiation of ART. In a retrospective review of 1.8 million patients with a cohort of 6500 HIV-positive patients, a significant cancer-specific morality was observed for colorectal, lung, melanoma and breast cancers.[11,12,13]

Diagnosis and staging of GTN [1,2,4-6]

The criteria for GTN diagnosis include any of the following:

- 4 or more human chorionic gonadotrophin (hCG) levels that plateau over 3 weeks
- 10% hCG increase in more than 3 levels over a 2-week period
- Histological confirmation of choriocarcinoma
- hCG > 20 000 IU/L 4 weeks post-evacuation
- Post-evacuation bleeding that is not due to retained tissue
- Detectable hCG levels 6 months post-evacuation of a molar pregnancy

Once the diagnosis for a GTN is established, evaluation for systemic disease is pursued. Staging investigations include a chest X-ray, transvaginal sonar, abdomen-pelvis computer tomography (CT) and, if vaginal and/or lung metastases is present, a brain CT or a magnetic resonance image (MRI) is recommended **(Table 1).** The role of positron emission tomography (PET) in staging of GTN is unclear but may be useful in detecting resistant disease sites or lesions for possible resection.

Patients are staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification and then allocated a WHO risk-score.

Table 2: Figo staging for GTN[1-6]

FIGO Stage	Description
I	Tumours strictly confined to the uterus corpus
II	Tumours extending to the adnexae or vagina, but limited to the genital structures
III	Tumours extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

Table 3: WHO scoring system based on prognostic factors[1-6]

Risk factor	0	1	2	4
Age	< 40	> 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	< 4	4–6	7–12	> 12
Pretreatment hCG IU/mL	$< 10^3$	$> 10^3$–10^4	$> 10^4$–10^5	$> 10^5$
Largest tumour size including uterus, cm	-	3–4	≥ 5	-
Site of metastases including uterus	Lung	Spleen, kidney	GIT	Brain, liver
Number of metastases identified	-	1–4	5–8	> 8
Previous failed chemotherapy	-	-	Single drug	≥ 2 drugs

The risk-category helps to guide management with either single agent or combination chemotherapy. A WHO risk-score of ≤ 6 is regarded low-risk and patients are managed with single agent chemotherapy. A score of ≥ 7 constitutes high-risk and it is unlikely that this group of patients will be cured with a single agent; therefore, combination chemotherapy is the recommended standard. A grey-zone exists around a count of 5–6 and/or a clinicopathological diagnosis of choriocarcinoma; single agent therapy might cure some but careful follow-up is

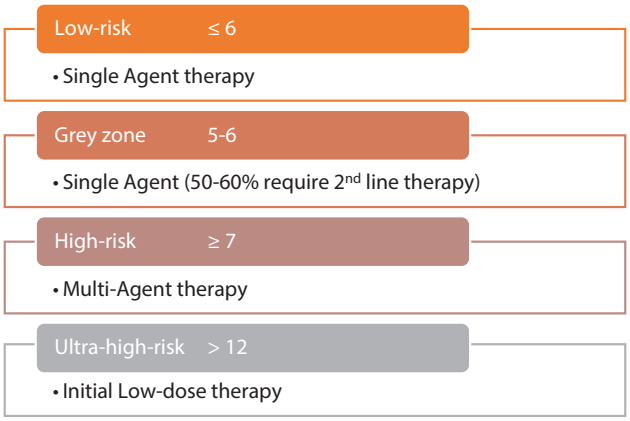
Table 1: Evaluate for metastases

Modality	Organ	Incidence
Chest X-Ray CT optional	Lung present as: • Discrete round nodules • Snowstorm pattern • Pleural effusion • Pulmonary Arterial occlusion	80%
CT Abdomen-pelvis	Liver, Kidney, GIT, Spleen	10%
Pelvic Sonar	Vagina, lower genital tract	30%
MRI or CT	Brain	10%
Lumbar Puncture (LP)	Occult cerebral or meningeal disease	
Blood work FBC U&E; LFTs Thyroid HIV/VL Clotting profile Serial hCG	Nephrotic syndrome [PSTT or ETT] If hCG > 100 000 IU/mL [Thyroid storm]	
PET	Identify potentially resectable lesions	

CXR: Chest X-Ray; CT: Computer Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; hCG: human chorionic gonadotrophin; HIV Eliza test; VL: Viral Load

necessary, as 50–60% of these patients will require second-line chemotherapy for cure.[1-6]

Ultra-high-risk disease includes extensive liver, lung or brain metastases, a FIGO score of more than 12, major bleeding, and a hCG level in excess of 1 000 000IU/L. Early deaths occur within 4 weeks of treatment and are mostly due to respiratory compromise because of haemorrhage within the thorax, intraperitoneal or intracranial spaces, and secondary to the tumour burden and resultant rapid tumour destruction that occurs with chemotherapy. Hence the introduction with low-dose therapy (LD) that gradually reduces tumour volume and associated tumour oedema. The LD-EP regime, consisting of Etoposide 100 mg/m^2 and Cisplatin 20 mg/m^2 intravenously on days 1 and 2, given weekly till patients are clinically stable, has increased the already good overall survival by a further 9% by preventing early deaths that occur with life threatening disease.[1,2,4,14]



Management

The diagnosis and management of GTN in PLWH requires a multidisciplinary team that includes the gynaecologist (suction curettage, and/or total abdominal hysterectomy), an HIV clinician, oncologist, chemotherapy nurse, social worker and auxiliary services. Pharmacists, oncologists and HIV clinicians all need to review cancer treatment for possible drug-interactions and overlapping toxicities.

Indication for chemotherapy [1,3,4-6]	
Post-evacuation hCG	After 4 weeks hCG level still > 20 000 IU/L hCG not falling after 4 months 6 months even if hCG is still falling
Metastases	Liver, lung, vulva, vagina Any other site
CXR	Lesions > 2 cm
Bleeding	Vaginal, GIT or Intraperitoneal
Choriocarcinoma	Present

The choice of chemotherapy depends on the FIGO-WHO Prognostic score and risk groups, disease stage, and previous drug exposure. Remission is regarded as 3 consecutive normal hCG levels over a 14 to 21 day period. A normal hCG level requires 3 additional cycles of therapy – trials confirmed that 2 versus 3 cycles of consolidation therapy showed a doubling in recurrence rate, thus 3 additional cycles is regarded standard of care. Low blood counts do not mandate to delay or reduce dose unless complications with febrile neutropenia or a significant clinical event occurs. Colony stimulating factors (GSF) as secondary prophylaxis with G-CSF on days 3–6 and 9–14 with the EMA/CO regime help to maintain dose-dense therapy and prevent neutropenia.

Treatment recommendation by stage

M: Methotrexate; A: Actinomycin; E: Etoposide; C: Cyclophosphamide; O: Vincristine; P: Cisplatin; T: Paclitaxel; G: Gemcitabine

FIGO Stage	Risk	Treatment	Salvage	Cure Rate
I	Low	TAH & 1 x MTX Single agent MTX/Actinomycin	Actinomycin MTX MAC EMA	> 90%
II	Low	Single agent Actinomycin/MTX	MAC EMA	> 80%
III	High	EMA/CO	EMA/EP Surgery	79%
IV	High	EMA/CO	EMA/EP TP/TE GP	40–60%

Literature review

Literature search reveals single institute publications of case studies for GTN and PLWH. To date, there is no evidence that GTD is more prevelant in patients with HIV. As far back as 1996, Rolansky et al. observed gynaecological neoplasms in HIV-positive patients were more resistant to chemotherapy and appeared to have a poorer prognosis.[15] In a retrospective review by Moodley et al. 78 patients were diagnosed with GTD, with a HIV seroprevalance of 31%. Among the HIV-positive patients who received chemotherapy and demised, the cause of death included widespread disease, multiorgan failure, and toxicity due to chemotherapy. Their findings also highlight the poor outcome of PLWH with a CD4 count less than 200 cells/µL, poor chemotherapy tolerance or performance status that precluded the administration of chemotherapy.[16]

Tayib et al. published a 10-year, single institute, retrospective review of 76 GTN patients with an 18.4% cohort that was living with HIV infection. They conclude that more advanced stage, HIV seropositivity and poor complaince with treatment also portend poorer outcomes in GTN patients.[17]

In a 2002 published case presentation (Ashley) with a literature review, only four cases of PLWH and choriocarcinoma had been reported. Low CD4 counts in HIV infection lead to poor outcome despite chemotherapy treatment and immunodeficiency can influence the course of treatment and outcome of patients.[18] In an East African report, Olwang and colleagues argue that HIV infection may predispose patients to extensive metastatic choriocarcinoma and influence the course of treatment, and proposed that HIV infection be considered a poor prognostic risk for GTN.[19]

Real world challenges

In developing and middle-income countries, socio-economic issues play a major role in the management of HIV-positive women diagnosed with GTN. In many societies women are the sole breadwinner of households and loss of workdays due to treatment lead to loss of income and poor treatment compliance. Lack of transport and financial resources contribute to poor treatment compliance as many women rely on public transport for hospital visits to specialized treatment centres.

Bed availability in hospitals make continuous infusion regimes problematic and 5-day Methotrexate versus pulse Actinomycin; EMA/CO [Day 1, 2, and day 8] *versus* MAC [Day 1 - 5 every 3 weeks] *versus* BEP [Day 1 - 5 every 3 weeks] offer alternative chemotherapy choices for the patient. The HIV burden in newly diagnosed patients with associated low CD4 counts versus patients who are established on ART and the potential drug interactions make for challenging treatment decisions. In HIV-positive patients with poor CD4, little clarity is available whether ART should commence speedily and the administration of chemotherapy delayed until immune reconstitution occurs. HIV and associated co-infections, e.g. pulmonary tuberculosis, cytomegalovirus and hepatitis infections, remain a challenge in the clinic.

PLWH generally present with advance stage presentations with multiple lung and brain metastases. Both HIV and GTN have haematological complications with the potential risk of secondary infections and associated morbidity and mortality. Immunosuppression and low CD4 counts with poor performance status predict a poor response and tolerability to chemotherapy. Response to GTN is generally favourable but in PLWH and immune suppression, outcome is compromised due to treatment delays, haematological toxicity and secondary infections that contribute to poor tolerability and response to treatment with a resultant poor prognosis.

Conclusion

PLWH should be offered the same cancer therapy as HIV-negative individuals and no cancer treatment modifications should be made solely on the basis of HIV status. Care should be co-managed with both the oncologist and HIV specialist. Response to treatment for GTN is generally favourable; the overall cure rate for GTN is 90% but the sequalae of HIV, the resultant low CD4 counts, comorbidities, poor performance status and extend of metastatic disease in patients receiving chemotherapy, compromise prognosis and survival.

Acknowledgement and disclosure: No conflict of interest is declared. No funding was received for this review.

References

1. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynecol Obstet. 2018;143(suppl.2):79-85. DOI:10.1002/ijgo.12615
2. Brown J, Naumann RW, Seckl MJ, Schink J. 15 years of progress in gestational trophoblastic disease: Scoring, standardization, and salvage. Gynecol Oncol. 2017;144:200-7. DOI:10.1016/j.ygyno.2016.08.330
3. Lurein JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. AJOG. 2010;531-9. DOI:10.1016/j.ajog.2010.06.073
4. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;1-12. DOI:10.1093/annonc/mdt345
5. Jordan SE, Papatla K, Hernandez E. Gestational trophoblastic neoplasia. Topics in obstetrics and gynecology 2017;37(6):1-5.
6. Tse KY, Chan KL, Ngan HY. An update on gestational trophoblastic disease. Obstet Gynecol Reprod Med. 2011:22(1):7-15.
7. UNIAIDS Data 2017. UNIADS Global Report. Available from: http://www.unaids.org
8. Spano JP, Atlan D, Breau JL, Farge D. AIDS and non-AIDS-related malignancies: a new vexing challenge in HIV-positive patients. Europ J Inter Med. 2002;13:170-9.
9. Wroblewska I. Non-AIDS-defining cancers in the light of recent research. HIV & AIDS Review. 2010;9:7-10.
10. Suneia G, Lin CC, Simard EP, Han X, Engels EA, Jemal A. Disparities in cancer treatment amongst patients infected with the human immunodeficiency virus. Cancer. 2006;122(15);2399-2407. DOI:10.1002/cncr.30052
11. Coghill AE, Shiels MS, Suneia G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol. 2015;33(21):2376-83. DOI: 10.1200/JCO.2014.59.5967
12. Patel P, et al. Incidence of types of cancer amongst HIV-infected persons compared with the general population in the US, 1992-2003. Ann Intern Med. 2008;148:728.
13. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer and mortality rates and trends. Review: cancer surveillance research. Cancer Epidemiol Biomarkers Prev. 2010;19(8):1893-907. DOI:10.1158/1055-9965.EPI-10-0437
14. Alifrangis C, Agarwal R, Short D, et al. EMA/CO for High-risk Gestational Trophoblastic Neoplasia: Good outcomes with induction Low-dose Etoposide-Cisplatin and Genetic analysis. J Clin Oncol. 2012:31(2);1817-23.
15. Rolanski N, Anteby SO. Gynecological neoplasias in the patient with HIV infection. Obstet Gynecol Surv. 1996;51(11):679-83.
16. Moodley M, Budhram S, Connolly C. Profile of mortality amongst women with GTD infected with HIV: argument for a new poor prognostic factor. Int J Gynecol Cancer. 2009;19:289-93. DOI: 10.111/IGC.0b013e31819bd212
17. Tayib S, van Wyk L, Denny L. gestational trophoblastic neoplasia and human immunodeficiency virus infection. Int J Gynecol Cancer. 2011;21:1684-2691. DOI:10.1097/IGC.0b013e31822d8ffd
18. Ashley I. Choriocarcinoma in a patient with human immunodeficiency virus: case presentation and review of the literature. Mt Sinai J Med. 2002;69(5):334-7.
19. Olwang SB, Otieno MR, Khan KS. Human immunodeficiency virus in gestational trophoblastic neoplasias - is it a poor prognostic factor. East Afr Med J. 1992;69(11):647-8.