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ORIGINAL ARTICLE

Uterine Artery Pulsatility Index as an Emerging Promising Marker in the Management of Gestational Trophoblastic Neoplasia

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ABSTRACT

Objective: Increasing new blood vessel formation (neoangiogenesis) within tumors is one of the adverse prognostic factors for survival in several cancers. Neoangiogenesis *in vivo* can be assessed by Doppler ultrasonography by measuring uterine artery pulsatility index (UAPI) in patients with gestational trophoblastic neoplasia (GTN). In this study we assessed whether UAPI can be an independent prognostic factor predictive of response to chemotherapy.

Methods: This was a prospective observational study conducted in Medical College, Kolkata from May 2011 to December 2012. Twenty-two patients of GTN had their FIGO prognostic scoring done, 19 patients were of low risk (scored ≤6) and three patients were of high risk (score > 6). The 3 high risk GTN patients were excluded from the study. The study population therefore consisted of 19 low risk (scored ≤6) patients of GTN who were treated with fortnightly cycles of 50 mg of methotrexate IM on days 1, 3, 5 and 7 and with 15 mg of folinic acid rescue IM on days 2, 4, 6 and 8. Treatment was continued in all patients till hCG values were negative and 2 further cycles of chemotherapy were given. The patients were followed up with UAPI and serum β-hCG levels every 2 weeks following chemotherapy to assess whether fall in β-hCG correlated with rise in UAPI values following chemotherapy. Data collected were analyzed using standard statistical protocol.

Results: The β-hCG concentration of these patients at the time of diagnosis ranged from 1400 to 210,000 mIU/ml and UAPI varied from 0.47 to 2.1. The mean β hCG of these 19 patients before chemotherapy (week 0) was 63705.47 mIU/ml and subsequently following chemotherapy at the end of 16 weeks was 1.64 mIU/ml. The mean UAPI before chemotherapy (week 0) was 1.33 and following chemotherapy at the end of 16 weeks was 1.952. All patients achieved complete remission with chemotherapy. The fall in beta-hCG levels corelated with the rise in UAPI values.

Conclusion: This study provides proof of principle that the UAPI can serve as a noninvasive *in vivo* measure of functional tumor vascularity, which independently can predict the response to chemotherapy.

Keywords: Gestational trophoblastic neoplasia, Neoangiogenesis, Neovascularization, β-hCG, Uterine artery pulsatility index.

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INTRODUCTION

Neoangiogenesis is a common feature of malignancy. Many immunochemistry studies have shown that neoangiogenesis is an independent adverse prognostic factor for different tumors.[1-3] Doppler ultrasound has provided a unique method for noninvasive study of this neovascularization. Doppler USG is a widely available, cheap technique to assess changes in larger vessels supplying tumors. Gestational trophoblastic disease (GTD) is an umbrella term for a group of pregnancy related disorders arising from abnormal placental trophoblast cells. It encompasses two premalignant conditions-partial and complete hydatidiform moles and the malignant gestational trophoblastic neoplasias (GTN)-invasive mole, choriocarcinoma and the very rare placental site trophoblastic tumor. GTN including invasive mole and choriocarcinoma originate in the uterus and provide an excellent example of a richly vascularized neoplasm.[4] As part of the routine staging of this disease, all patients undergo Doppler USG of the pelvis to assess uterine volume and blood flow through uterine arteries. The latter is used to calculate the uterine artery pulsatility index (UAPI). The UAPI reflects impedance to blood flow within the uterus or tumor. A low UAPI indicates increased arteriovenous shunting, probably associated with neovascularization found in GTN[5] and might therefore be expected to be an adverse prognostic factor. Subsequently gradual rise of UAPI during chemotherapy indicates diminution of vascularization of the tumor as a good response to drugs. So UAPI can also be an independent predictor of response to chemotherapy. Consequently in this study we measure UAPI as an indirect *in vivo* measure of neoangiogenesis and whether it can predict the response to chemotherapy in patients of GTN.

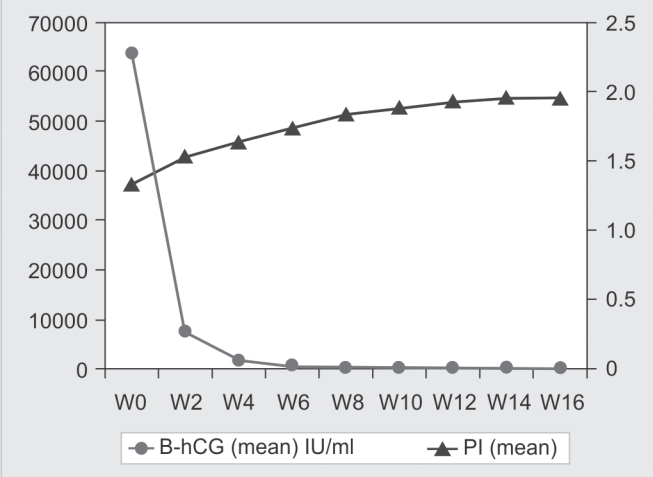
MATERIALS AND METHODS

The study was conducted at Gynecology and Obstetrics Department of Medical College and Hospital, Kolkata from May 2011 to 31st December 2012. It was a prospective observational study. Out of 76 patients of GTD who attended our hospital in the above period, 22 patients were diagnosed as cases of GTN on the basis of thorough history, clinical examination, investigations (serum β-hCG, chest X-ray and sonography) and histopathological report (where available). All patients of GTN had their FIGO prognostic scoring done — 19 patients were of low risk (scored ≤6) and three patients were of high-risk (score > 6). All these patients required chemotherapy, however high-risk GTN patients (FIGO

prognostic score > 6) who required combination chemotherapy were excluded from the study. The study population therefore consisted of 19 low risk (scored ≤6) patients of GTN who were treated with fortnightly cycles of 50 mg of methotrexate IM on days 1, 3, 5 and 7 and with 0.1 mg/kg of folinic acid rescue IM on days 2, 4, 6 and 8.[5,6] Treatment was continued in all patients till β-hCG values were negative and two further cycles of chemotherapy were given as per Charing Cross Hospital protocol. The patients were followed up with UAPI and serum β-hCG levels every 2 weeks during chemotherapy to assess whether fall in β-hCG correlates with rise in UAPI values following chemotherapy. All patients were followed up for 16 weeks to maintain uniformity in our study. Data collected were analyzed using standard statistical protocol.

OBSERVATIONS

Seventy-six patients of GTD attended our hospital from May 2011 to 31st December 2012. GTN was diagnosed among 22 patients (28.9%) of which 19 patients (86.4%) were of low risk (scored ≤6) and treated with single agent chemotherapy (methotrexate and folinic acid) and 3 patients (13.6%) were of high risk (score > 6) and required combination chemotherapy (EMA-CO). However, high risk patients were excluded and 19 low risk GTN patients were finally included in the study. Most of these patients were in the age group 20 to 40 years (73.7%) and the incidence was comparatively seen to be more in primigravida (36.8%) and 4th gravida (31.6%). The β-hCG concentration of these patients at the time of diagnosis ranged from 1400 to 210,000 mIU/ml and UAPI varied from 0.47 to 2.1. The mean β-hCG of these 19 patients before chemotherapy (week 0) was 63705.47 mIU/ml and subsequently following chemotherapy at the end of 16 weeks, mean β-hCG was 1.64 mIU/ml (vide Table 1). The mean UAPI before chemotherapy (week 0) was 1.33 and following chemotherapy at the end of 16 weeks was 1.952 (vide Table 1). None of these patients had received any prior chemotherapy, either therapeutic or prophylactic for GTN. All patients achieved complete remission with chemotherapy. The fall in β-hCG levels corelated with the rise in UAPI values (Graph 1).



Graph 1: Correlation between mean β-hCG and mean UAPI values

DISCUSSION

The present clinical study was done to measure UAPI as an indirect *in vivo* measure of neoangiogenesis and whether it can predict the response to chemotherapy in patients of GTN. Due to arteriovenous shunting, molar tissue has a low resistance circulation. Doppler studies calculating the UAPI can measure the degree of shunting. UAPI also may be the independent predictor of response to chemotherapy for GTN. Low UAPI is an adverse predictor where as gradual rise of UAPI indicating a good response.[7] The present study also showed the mean β-hCG of these patients before chemotherapy (week 0) was 63705.47 mIU/ml and the mean UAPI was 1.33 and subsequently following chemotherapy at the end of 16 weeks mean β-hCG was 1.64 mIU/ml and the mean UAPI was 1.952 respectively. In our study, all patients achieved complete remission with chemotherapy and the fall in β-hCG level corroborated with the rise in UAPI values. Doppler USG may provide a useful method for *in vivo* functional assessment of tumor vasculature by assessing hemodynamic changes in the microvasculature as an indirect reflection of the microvasculature (vessel diameter <15 micrometer) used to define neoangiogenesis.[8] UAPI measures impedance to blood flow in the main arteries supplying the uterus/GTN. A falling UAPI co-relates with increasing neoangiogenesis associated with an enlarging uterus or tumor volume and rising hCG concentration.[9-11] Assessment of UAPI have diagnostic[12] as well as prognostic roles in the management of GTN. The serial UAPI measurements after molar evacuation also can be utilized to identify patients who will develop GTN earlier than total hCG levels.

CONCLUSION

The most important advances in modern gynecology and obstetrics are Doppler ultrasound. Its simplicity and ease of operation changed the way we practice gynecology.

This study provides proof that the UAPI can serve as a noninvasive *in vivo* measure of functional tumor vascularity, which independently predicts the response to chemotherapy. There is a clear need to develop *in vivo* methods for assessing tumor vascularity because this has the potential to predict

Table 1: Correlation between mean beta-hCG and mean PI values of 19 patients through weeks 0 to 16

No. of weeks	*Weeks 0*	*Weeks 2*	*Weeks 4*	*Weeks 6*	*Weeks 8*	*Weeks 10*	*Weeks 12*	*Weeks 14*	*Weeks 16*
beta-hCG (mean)	63705.47	7629.68	1813.37	574.0	224.48	79.36	31.45	8.75	1.64
PI (mean)	1.33	1.53	1.64	1.74	1.84	1.88	1.92	1.95	1.952

prognosis and to determine the most beneficial type of therapeutic strategy in patients with cancer.

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