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Blood flow in the site of invasive moles within the myometrium after completion of chemotherapy: retrospective study of 33 patients

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Summary

Objectives: Women with invasive moles (IMs) should continue with one or two cycles of chemotherapy until the level of human chorionic gonadotrophin (hCG) concentrations become normal. However, assessment of blood flow (BF) with Doppler ultrasonography (DU) in the myometrial mass after chemotherapic completion has not been reported. *Materials and Methods:* We intended to find out the outcomes of BF associated with different treatments during following-up by DU. The patients were employed different treatments (resection, chemotherapy or following-up). We use the Kaplan-Meier method to perform survival analysis between different groups. *Results:* Of 33 cases, two patients underwent resection of the mass, five patients had 1–2 additional cycles of chemotherapy, and the other 26 subjects had follow-up without additional treatment. There were no significant differences in initial hCG values, chemotherapy cycles, risk scores for IM, and diameter of masses between the two groups. However, differences in BF disappearance time in the two groups were detected, and hCG levels did not increase again in the two groups. *Conclusions:* These data suggest that IM patients can be followed up if DU reveals BF within masses in the uterine myometrium after completion of chemotherapy.

Key words: Doppler ultrasonography, invasive moles, blood flow, follow-up, hCG, retrospective study.

Introduction

A hydatidiform mole (HM) can result in pregnancies with excessive proliferation of placental villi but severely stunted/absent embryonic development. A HM should be regarded as a pre-malignant lesion because 15%–20% of complete HMs and 1% of partial HMs undergo malignant transformation into invasive moles (IMs), choriocarcinomas or, rarely, placental-site trophoblastic tumors or epithelioid trophoblastic tumors [1,2]. IMs are the most common gestational trophoblastic tumors [3-5].

Until now, prediction of which HMs will undergo malignant transformation has not been possible. Recently, a few reports found genetic disorders in IMs, and this information could be helpful for prediction of the malignant transformation of HMs [6-8]. In the clinic, IMs are usually diagnosed if patients have persistent elevation of human chorionic gonadotropin (hCG) levels after mole excision, and are frequently treated with chemotherapy without a histopathologic diagnosis. For low-risk IMs (score, 0–6), the regimen is usually methotrexate; for high-risk IMs (score, ≥7) a combined regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine (EMA-CO) or KSM+5-FU) is employed [1,9-11]. Patients with a diagnosis of IM usually have excellent outcomes during or after primary chemotherapy, and ≈100% of low-risk and 84% of high-risk patients are cured [1,9-11]. After hCG concentrations drop to normal levels in these patients, administration of additional chemotherapy is related to the speed of decline of hCG levels, the level of hCG, and risk factors for IMs. Usually, an additional cycle of chemotherapy for low-risk IMs and 1–2 additional cycles of chemotherapy for high-risk IMs can be administered [1,9-11]. However, in some IM patients, Doppler ultrasonography (DU) reveals blood flow (BF) within the uterine myometrium after completion of conventional chemotherapy. The dilemma is what should be done: simple follow-up, continued chemotherapy, or resection of the mass?

In the present study, we investigated the BF within masses in the uterine myometrium detected in 33 patients with IMs and negative hCG after chemotherapy, and the outcomes under different treatments.

Materials and Methods

The study protocol was approved by the Ethics Committee of Hubei University of Medicine, (Hubei, China), which acted as the central Ethics Committee for the study.

This was a retrospective study in which patients were diagnosed with IM with known BF within the myometrium and who became hCG-negative after chemotherapy. This study was conducted at Renming Hospital in Shiyan and the Second Affiliated Hospital of Xi'an Jiaotong University in Xi'an, which are both in China.

A retrospective search was undertaken using the databases of these two hospitals from 31 November 2007 to 31 November 2012 to identify women diagnosed with IMs <6 months previ-

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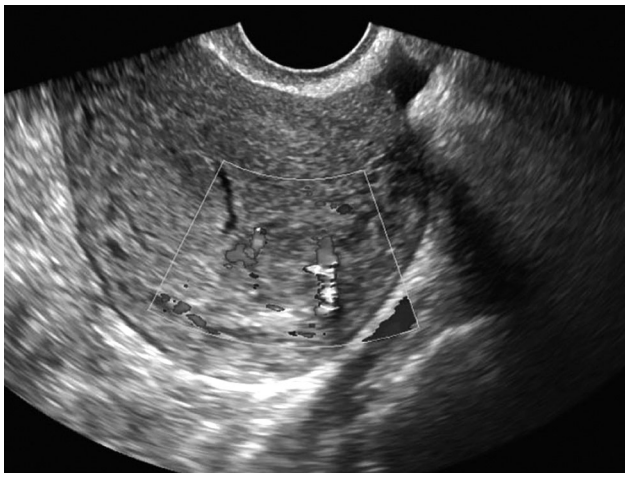

Figure 1. — Doppler ultrasonography shows blood-flow signals within a mass in the uterine myometrium after completion of chemotherapy in an IM patient.

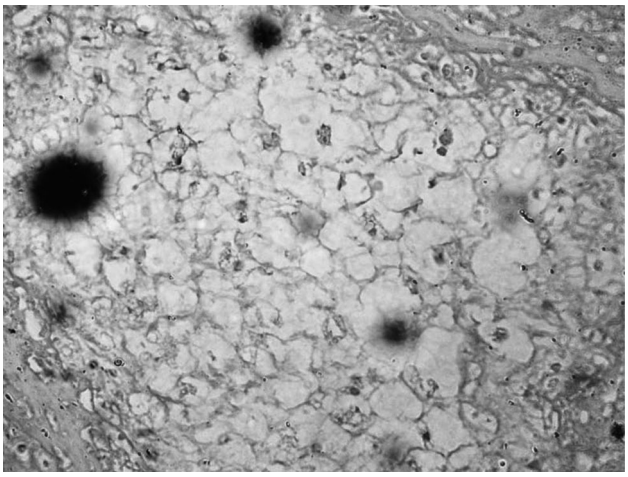

Figure 2. — Pathologic section suggests necrosis of a chorionic villus (magnification, ×400).

Table 1. — *Patient characteristics*

No.	Age (years)	Score	chemotherapy cycle	HCG Rebound[α]	Treatment	Time[β]	Pregnancy[γ] (year)
1	20	5	3	NO	Follow-up	4	NO
2	23	8	5	NO	Follow-up	5	1
3	30	9	6	NO	Resection + chemotherapy	3	2
4	26	4	3	NO	Follow-up	4	NO
5	22	5	3	NO	Follow-up	3	NO
6	19	12	7	YES	Follow-up	5	NO
7	22	10	6	NO	Follow-up	5	NO
8	27	13	6	NO	Follow-up	4	2
9	24	4	4	NO	Follow-up	4	NO
10	28	2	3	NO	Follow-up	4	2
11	30	4	3	NO	Follow-up	3	1.5
12	26	9	4	NO	Follow-up	4	NO
13	31	10	8	YES	Follow-up	24	2
14	27	11	6	NO	Follow-up	5	NO
15	25	10	7	NO	Follow-up	5	1.5
16	27	6	4	NO	Follow-up	6	2
17	18	3	5	NO	Additional chemotherapy	3	1.6
18	29	9	5	NO	Resection	4	1.9
19	23	10	8	NO	Additional chemotherapy	3	NO
20	22	5	4	NO	Follow-up	7	2
21	34	5	5	NO	Resection + chemotherapy	3	2
22	23	13	8	YES	Follow-up	4	NO
23	24	10	7	NO	Follow-up	4	NO
24	25	11	7	NO	Follow-up	6	NO
25	27	4	3	NO	Follow-up	6	2
26	25	5	4	NO	Follow-up	4	1
27	31	9	6	NO	Follow-up	6	NO
28	30	10	8	NO	Follow-up	5	0.9
29	32	12	8	NO	Additional chemotherapy	24	1.5
30	19	10	7	NO	Follow-up	6	NO
31	23	5	4	NO	Follow-up	5	2
32	25	5	4	NO	Additional chemotherapy	5	0.8
33	26	7	5	NO	Additional chemotherapy	6	1.2

α, HCG rebound during chemotherapy; β, blood flow signals disappearance after chemotherapy completion; γ, getting pregnancy after IM diagnosis

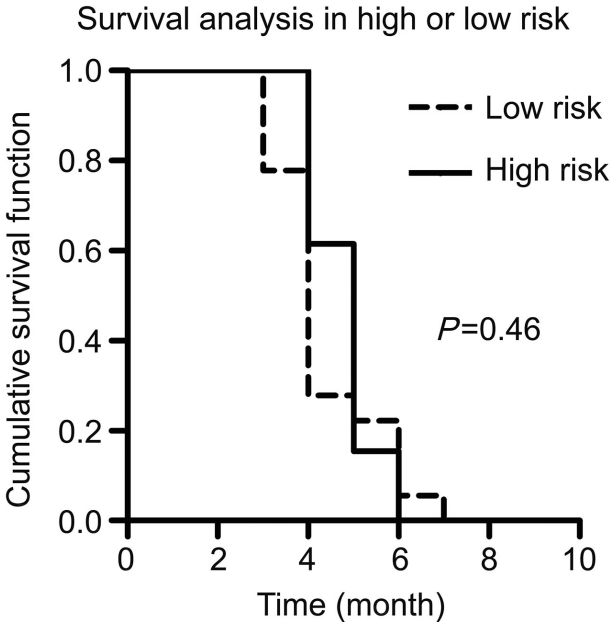

Figure 3. — Survival analyses based on high- and low-risk of contracting IM

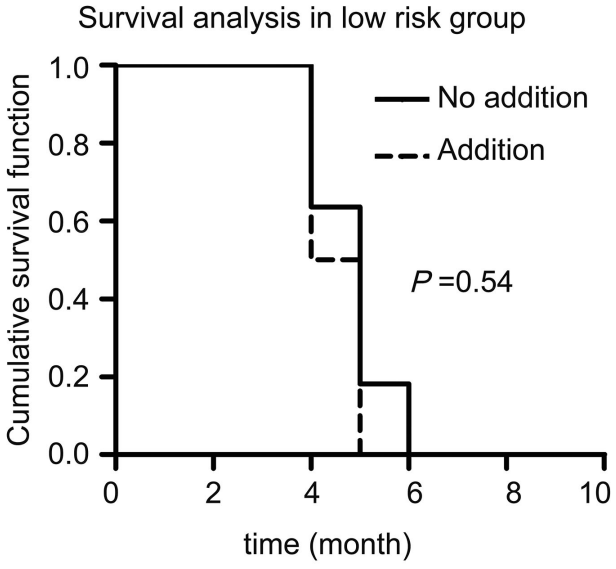

Figure 4. — Survival analyses based on additional chemotherapy after completion of chemotherapy.

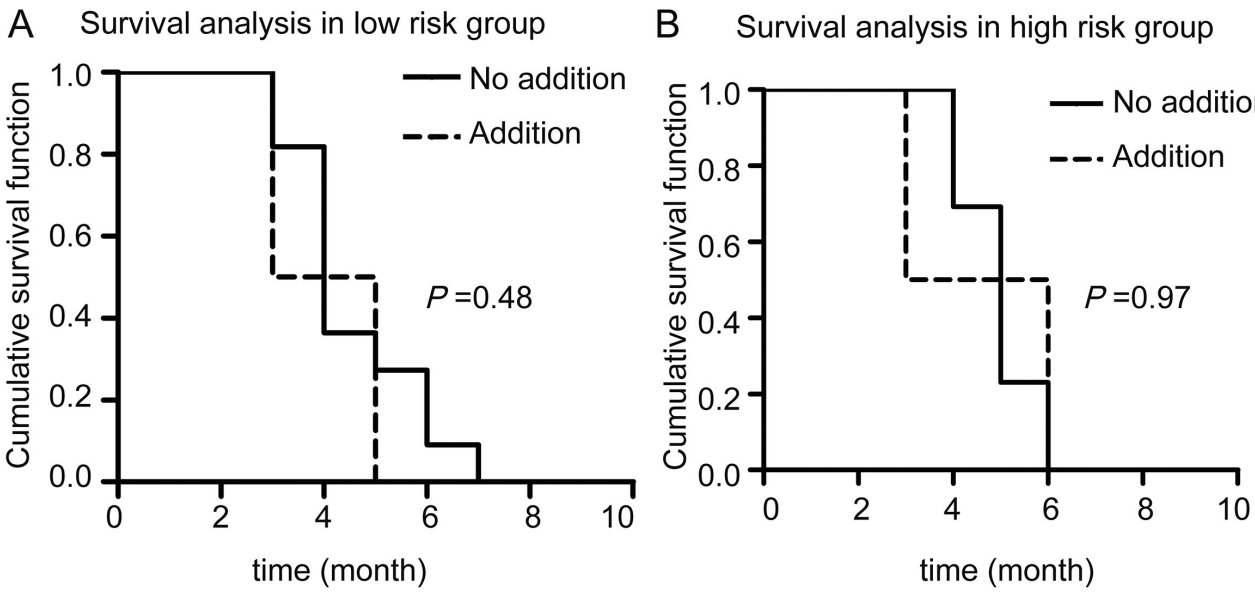

Figure 5. — Survival analyses based on hCG rebound during chemotherapy.

ously, all of who were followed up continually for >2 years. During follow-up, patients were tested for hCG concentrations every 2 weeks for the first 6 months, and then tested every month until 2 years. DU (5–7.5 MHz transvaginal transducer with spectral Doppler) was conducted each time with the hCG test by Yan Zhao.

Statistical analyses

On the basis of the inclusion criteria of our study, all patients who became pregnant must have demonstrated a blood flow disappearance time (BFDT) at the time of conception. Differences between the two treatment groups were assessed using a $\chi 2$ test or Fisher's exact test for categorical variables. An independent sample t-test was used for continuous variables. using the Kaplan-Meier method and were compared using nonparametric survival analysis (log-rank test). Survival curves were obtained All P values are two-sided, with $P<0.05$ considered significant. Statistical analyses were undertaken using SPSS v13.0.

Results

Patient characteristics

Thirty-three patients were found to have signals denoting BF within the invasion site (IS) of the uterus by DU and were recruited into the study (Figure 1). Patient characteristics are summarized in Table 1. BF signals lasted more than two years in two of the all patients. One of the patients became pregnant 18 months after she was diagnosed with IM, and BF disappeared after birth. The child was healthy and hCG become negative 2 weeks after delivery. IMs did not recur after primary chemotherapy in all patients. Two patients underwent resection at the IS within the myometrium. Five patients chose additional chemotherapy after they had completed conventional chemotherapy based on their risk scores and because hCG levels had declined rapidly during chemotherapy. Two patients became pregnant for less than one year after the diagnosis of IM, nine patients became pregnant less than two years after the diagnosis, and nine patients became pregnant >2 years from the diagnosis. All of their children were healthy and the hCG concentration declined to a normal level 2–3 weeks after delivery.

Necrotic placental tissues were found within the myometrium after resection of the IS

Two patients chose resection to remove the IS of the IM. The IS was located by DU before surgery. When the uterus was completely exposed during surgery, the IS of the IM within the myometrium was slightly purple and, compared with the surrounding myometrium, the IS was softer and thinner, protruding slightly into the outer muscle layer. The pathologic diagnosis of masses after resection was "necrotic placental tissue" (Figure 2).

No difference in BFDT in high- or low-risk groups

Except for the two patients with persistent BF within the IS, the surgical group and additional chemotherapy group, the remainder of patients were divided into the "high risk" group (13 patients) or "low-risk" group (11 patients) based on risk scores. BFDT within the IS was 4.55±0.39 months in the low-risk group and 4.78±0.21 months in the high-risk group. Survival analyses indicated no significant difference in BFDT in the two groups (P=0.46) (Figure 3).

Additional chemotherapy did not reduce the BFDT

After completion of chemotherapy cycles, five patients chose two additional cycles of chemotherapy because BFs were found within the IS by DU. Except for the two patients with persistent of BF within the IS and the surgical group, survival analyses indicated no significant difference in the BFDT between the additional chemotherapy group and follow-up group (Figure 4).

hCG rebound during chemotherapy was not associated with the BFDT

In the high-risk group, three patients were administered the EMA-CO regimen initially. Serum levels of hCG declined after chemotherapy and rebounded after 2–3 cycles of chemotherapy. We adjusted the paclitaxel-cisplatin + paclitaxel-etoposide (TP-TE) regimen for these patients as recommend for drug-resistant gestational trophoblastic tumors [11]. Their hCG levels continued to decline and did not rebound after adjustment of the chemotherapy regimen. The BFDT was not significantly different in the rebound group (5.13±0.21 months) or non-rebound group (5.02±0.23 months) (Figure 5).

Discussion

Levels of hCG in the serum of IM patients is the most important index in the follow-up period after the completion of chemotherapy [1,12]. If the hCG level remains normal, even if there is metastasis to the lungs or brain, IM patients should undergo follow-up and additional treatments (thermotherapy, resection) should not be provided [13-15]. However, guidelines for IM patients with BF signals within the IS after completion of chemotherapy are not available.

In the present study, we addressed the prognostic impact of BF within the myometrium even if hCG levels decrease to within normal ranges after completion of chemotherapy in IM patients. BF within the myometrium after hCG levels had declined to normal levels was not associated with detrimental outcomes. These findings suggest that BF within the myometrium after a diagnosis of IM with negative hCG levels could be considered safe in women. The BFDT was not associated with the risk score of IM or drug resistance in IM. Additional chemotherapy did not aid the BFDT, and follow-up did not increase the chance of IM recurrence.

Using arteriography, Boronow *et al.* in 1970 showed that excess vascularization of the myometrium can persist after chemotherapy for IM [16]. Their findings were confirmed by the pathologic diagnosis of necrotic placental tissue after resection in two of our patients. These findings strongly suggest that functional trophoblastic tissue was eradicated (hCG was absent) whereas blood supply to the tumor (as determined by DU) was perhaps not yet remodeled and returned to basal levels.

Previously, patients were recommended to consider becoming pregnant 2 years after they had competed chemotherapy [11]. Recently, it was found the timing of pregnancy is not associated with pregnancy outcome after complete cure of IM. Some patients become pregnant even <1 year after a diagnosis of IM and have healthy children [11]. In our study, nine patients became pregnant 2 years after a diagnosis of IM. Two of the nine patients became pregnant <1 year after a diagnosis of IM, and their children were healthy. Nevertheless, patients are recommended to become pregnant 1 year after a diagnosis of IM [9,11,12,17]. Importantly, one patient with persistent BF in the IS became pregnant 2 years after a diagnosis of IM and IM her baby was healthy. Our results suggest that BF within

the ISS is not a factor when considering future pregnancies.

The present study had limitations. We did not ascertain if metastases of IM were absent. If metastases of IM were present (e.g., lung, brain), and BF within metastases were observed, whether further therapy would be needed would merit investigation. Hence, we suggest that patients with metastases of IM should be followed up if the hCG level is negative.

Conclusion

The present study suggests that BF within masses does not protect against IM recurrence. Our study could help to direct treatment after BF within masses has been found after IM patients have completed chemotherapy.

Acknowledgments

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