ORIGINAL ARTICLES

Identification of chemotherapeutic refractory cases based on human chorionic gonadotropin values among patients with low-risk persistent trophoblastic disease treated with 8-day methotrexate-folinic acid

T. Shigematsu[1], *M.D., Ph.D.*; **T. Hirakawa**[1], *M.D., Ph.D.*; **H. Yahata**[1], *M.D.*; **T. Sonoda**[1], *M.D.*; **N. Kinukawa**[2], *M.S., Ph.D.*; **H. Nakano**[1], *M.D., Ph.D.*

[1]*Department of Obstetrics and Gynecology, Graduate School of Medical Sciences*
[2]*Department of Medical Information Science, Kyushu University Hospital, Fukuoka (Japan)*

Summary

Purpose: The aim of the present study was to establish the accurate cutoff points of post-treatment serum ß-hCG values in identifying chemotherapeutic refractory cases among patients with low-risk persistent trophoblastic disease (PTD) treated with 8-day methotrexate-folinic acid as the primary therapy.

Materials and methods: The values of serum ß-hCG measured before initiating treatment and weekly thereafter in 26 patients with low-risk PTD undergoing 8-day methotrexate-folinic acid treatment were analyzed. Thereafter, we determined the weekly cutoff points to identify the patient refractory for treatment by means of receiver-operating characteristic (ROC) plots analysis.

Results: The values of cutoff points in the pretreatment, the post-treatment 1st, 2nd, 3rd, and 4th week were 18.6, 15.0, 5.4, 3.4, and 2.0ng/ml, respectively, and the value of accuracy during these weeks was appropriate (> 80%). When using the cutoff points of one and two weeks after initiating treatment, the accuracy in identifying chemotherapeutic refractory patients was 87.5% and 88.0%, respectively, with the highest values exceeding 85%. The sensitivity and specificity at one week were 92.9 and 80.0%, respectively. Similarly, the sensitivity and specificity at two weeks were 93.3 and 80.0%, respectively.

Conclusion: These results suggest that the cutoff points of one and two weeks after initiating treatment are useful in identifying chemotherapeutic refractory patients among low-risk PTD patients, receiving 8-day methotrexate-folinic acid treatment.

Key words: Persistent Trophoblastic disease; Low-risk PTD; Methotrexate; Human Chorionic Gonadotropin.

Introduction

It is established worldwide that patients with persistent trophoblastic disease (PTD) should be enrolled in a regimen with methotrexate treatment when they are diagnosed with low-risk PTD and given treatments with chemotherapy [1-17]. Most physicians elucidate chemotherapeutic efficacy according to the measurement of the size of tracing lesions by means of various imaging diagnoses (e.g., X-rays including CT scans, ultrasonography) and also on the evaluation of serial values of human chorionic gonadotropin (hCG) after initiating methotrexate treatment. There has yet to be a report discussing precisely whether methotrexare is effective or not for patients with such PTD based on the serial levels of hCG after treatment. Some authors have reported that various chemotherapies including methotrexate for gestational trophoblastic disease tend to be ineffective when regression trends of the serial hCG levels are considered to be inadequate or the pretreatment hCG values exceed the determined thresholds [1, 4, 6, 11-14, 16, 18-25].

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When trying to identify patients as being refractory for methotrexate treatment as precisely and early as possible after initiating chemotherapy, physicians often alternate methotrexate with other chemotherapeutic regimens (e.g., MAC, EMA/CO) quickly, without adequate time given to evaluate the results.

In this study, we established accurate cutoff points of post-treatment serum ß-hCG values in identifying chemotherapeutic refractory cases among patients with low-risk persistent trophoblastic disease (PTD) treated with 8-day methotrexate-folinic acid as primary therapy.

Materials and Methods

During the period from January 1986 through December 2001, 26 patients were diagnosed as having low-risk PTD according to the scoring based on World Health Organization prognostic index score criteria [26] at Kyushu University Hospital.

Thereafter, all 26 patients were administered 8-day methotrexate-folinic acid treatment (methotrexate; 1mg/kg, day 1, 3, 5, 7, folinic acid; 0.1 mg/kg, day 2, 4, 6, 8.) as the primary therapy, biweekly, for a minimum of two times (range 2-9 times, median 5). They all had measuring lesions of the uteri and/or lungs (10 uterus, 12 lung, 3 both uterus and lung) or in

the parametrium. After initiating treatment, the size of the lesion was measured monthly as a rule, by means of CT scans, until either the lesion disappeared or reached a level of no change (NC) or progressive disease (PD), according to the criteria of the Japan Society for Cancer Therapy (shifted to the criteria of the Japan Society of Clinical Oncology in 1997) [27].

The value of serum ß-hCG which was assayed by means of a radioimmunoassay kit using antiserum raised in rabbits against the ß-subunit of hCG (CIS Co-op, France) was also measured in all patients weekly after initiating treatment. Among the 26 patients, the tracing lesions in 11 patients disappeared completely within 4-16 weeks (median 11) after initiating methotrexate treatment. There have yet to be observed any lesions in these patients and the serum ß-hCG values in these patients remained at a level of less than 0.2 ng/ml (normal limit) for 1-15 years (median 9). These 11 patients were thus regarded as sensitive cases for methotrexate (Group 1).

According to the criteria of the Japan Society for Cancer Therapy, the remaining 15 patients had lesions considered to reach a level of no change or progressive disease within 4-18 weeks (median 10) after initiating methortrexate treatment and were thus alternated with other chemotherapeutic regimens (5 patients before 1988 year: ActinomycinD [12μg/kg, day 1~5], ten patients since 1988 year: EMA/CO [etoposide; 200 mg/m^2, methotrexate; 300 mg/m^2, actinomycin D; 1.0 mg cyclophosphamide; 600 mg/m^2, vincristine; 1.0 mg/m^2]). These 15 patients have had no lesions, with normal serum ß-hCG levels for 1-15 years (median 8) since completing salvage chemotherapies following methotrexate treatment, and were thus regarded as refractory cases for methotrexate (group 2).

Statistical analysis was also done using the statistical package BMDP LR (Los Angeles, CA) on SPARC station 20 (Mountain View, CA). The weekly serum ß-hCG values in the 11 patients defined as group 1 and those in the 15 patients defined as group 2 were plotted respectively. The significance of the differences in the values of serum ß-hCG at each week after initiating treatment between the two groups was calculated using the logistic regression analysis with logarithmic transformed values of the serum ß-hCG. A p value < 0.01 was considered to be statistically significant. Therefore the most appropriate cutoff value of the serum ß-hCG was chosen as the "cutoff point" for each week, when it was examined using receiver-operating characteristic (ROC) plot analysis to obtain the optimial diagnostic accuracy [28]. Any case in group 2 was included in "true positive" when its value of serum ß-hCG exceeded the cutoff point for each week. On the other hand, any case in group 1 was included in "true negative" when its serum ß-hCG reached a level below the cutoff point. The sensitivity, specificity and accuracy for each week were thus calculated.

We administered the regimen two times, four weeks after initiating it. Therefore we discussed the weekly cutoff points within four weeks after initiating treatment for the purpose of anticipating the chemotherapeutic efficacy of this regimen.

The values for each week were obtained for each specific week, for instance, week 3 = from 21 to 27 days after initiating treatment. However, the values at 0 week were obtained within 1-2 days before initiating treatment.

Results

The average serum ß-hCG value of the 11 patients defined as group 1, before treatment, was 40.7 ng/ml and ranged from 0.3 to 287 ng/ml, while the average of the 15 pre-treatment serum ß-hCG concentrations in the patients defined as group 2 were 272.3 ng/ml and ranged from 7.2 to 1020 ng/ml. The weekly values of the serum ß-hCG obtained from both group 1 and 2 respectively, and the "cutoff point" for each week made using the previously described method, are shown in Figure 1.

Table 1 shows the sensitivity, specificity and accuracy when a cutoff point is established for each week, in order to identify the PTD patients refractory for 8-day methotrexate-folinic acid treatment. Accuracy values exceeded 80% for all weeks after treatment. At one and two weeks, accuracy was particularly high, 87.5% and 88.0%, respectively, with the highest values exceeding 85%. When using the cutoff point of one week after treatment, the sensitivity and specificity in identifying patients as refractory for chemotherapy were 92.9 and 80.0%, respectively. Similarly, sensitivity and specificity at two weeks were 93.3 and 80.0%, respectively.

On the other hand, 3/15 (20%) of group 2 was diagnosed as refractory for treatment by means of CT scan at four weeks after treatment.

Table 1. — *Sensitivity, specificity and accuracy for each weekly cutoff point in identifying chemotherapeutic refractory PTD patients.*

Week	0 (n = 26)	1 (n = 24)	2 (n = 25)	3 (n = 23)	4 (n = 26)
Cutoff point (ng/ml)	18.6	15.0	5.4	3.4	2.0
Sensitivity (%)	86.7	92.9	93.3	83.3	80.0
Specificity (%)	72.7	80.0	80.0	81.8	90.9
Accuracy (%)	80.8	87.5	88.0	82.6	84.6
p value	0.0016	0.0001	0.0001	0.0004	0.0001

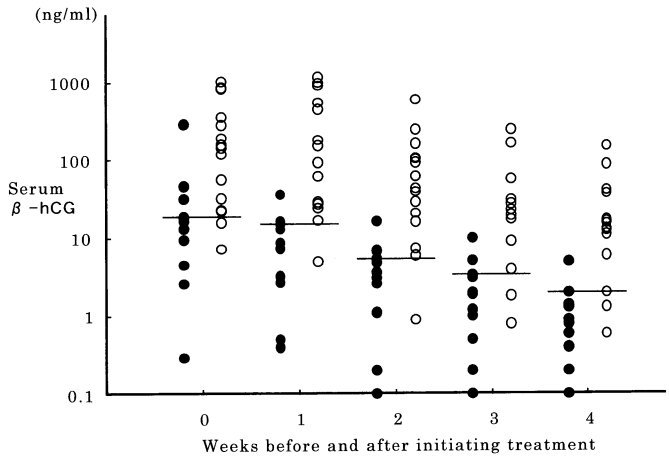

Figure 1. — The weekly serum ß-hCG values between two groups and the cutoff point before and after the 8-day methotrexate-folinic acid treatment.
● = weekly serum ß-hCG values in group 1 (sensitive cases for methotrexate); ○ = weekly serum ß-hCG values in group 2 (refractory cases for methotrexate); Bar = weekly cutoff point.

Discussion

Bagshawe *et al.* reported that folinic acid was useful in reducing the toxicity of methotrexate in 1964 [29].

Berkowitz *et al.* first described 8-day methotrexate-folinic acid administration in 1980 [15] and reported that 8-day methotrexate-folinic acid treatment should be the preferred primary treatment in low-risk PTD in 1982 [14]. Thereafter, 8-day methotrexate-folinic acid treatment has been administered as primary therapy for patients with low-risk PTD in our institution since 1986 while various regimens on methotrexate-folinic acid treatment have since been reported [1-13, 16-17].

In this study, for the purpose of establishing a method identifying chemotherapeutic refractory PTD patients for methotrexate treatment based on hCG values, we analyzed hCG values in 26 patients who had such eligibilities as 1) categorized as low-risk PTD, 2) treated with 8-day methotrexate-folinic acid regimen primarily, 3) having measurable lesions and followed periodically by CT scan and 4) have had serum ß-hCG measured both before treatment and weekly thereafter. Afterwards, we determined the weekly cutoff points before and after initiating the 8-day methotrexate-folinic acid regimen, by means of receiver-operating characteristic plot analysis. These cutoff points were the most appropriate values based on hCG, to optimize diagnostic accuracy, when identifying the chemotherapeutic refractory patients among low-risk PTD patients who were clarified as to sensitive or refractory for methotrexate by means of measuring their follow-up lesions, retrospectively. The present study led to the understanding that, the cutoff points at one and two weeks after initiating treatment, were appropriate to identify chemotherapeutic refractory PTD patients when accuracy values at those points had the highest values exceeding 85%.

Newlands *et al.* described that response to a chemotherapy course was evaluated as the change in hCG value and thus defined chemotherapeutic efficacy as "a response" when hCG concentration showed a fall greater than one-log and defined "an improvement" when hCG values fell more than 50% [19]. Similarly, some authors reported that the hCG regression curve served as a reliable guide for elucidating chemotherapeutic efficacy during administration of methotrexate [11, 13]. In this study, while 33.3% of the 15 patients in group 2 were categorized as either "no response" or "progressive disease" after the completion of the first course of chemotherapy according to Newlands *et al.* [19] (data not shown), 92.9 and 93.3% of group 2 were identified as refractory at one and two weeks, respectively, after initiating treatment.

On the other hand, Gleeson *et al.* reported that among 25 low-risk PTD patients, all patients with pre-treatment ß-hCG of 650 mIU/ml (almost all corresponded to ß-hCG of 65 ng/ml) or less responded to primary methotrexate treatment, whereas 50% of those with higher levels required second-line chemotherapy [6]. Similarly, some authors highly regarded pretreatment hCG levels in order to anticipate whether PTD patients were sensitive or refractory for chemotherapies [4, 14, 12, 20, 23, 25]. In the present study, regarding pretreatment hCG levels, the values of accuracy at the cutoff point of 0 weeks were lower than those one week and two weeks after treatment.

In the current study, the majority of the patients refractory for this regimen, obtained serum ß-hCG values exceeding the weekly cutoff points. Several authors reported that patients with high-risk PTD were almost all refractory for such a single-agent chemotherapy as methotrexate. Therefore patients with high-risk PTD require either multiagent chemotherapy (e.g., EMA/CO) as the initial therapy or a cisplatin-based chemotherapy as salvage therapy [18, 21, 22, 24, 30-32]. These findings suggest that such low-risk PTD patients, having serum ß-hCG exceeding the weekly cutoff points, could have some but not an abundance of elements, biologically compatible with high-risk PTD patients, while the degree of biological compatibility extends variously. Therefore those patients were revealed as refractory for methotrexate and needed alternative chemotherapeutic regimens.

In conclusion, by using cutoff points at one and two weeks after initiating treatment, instead of evaluating either after-treatment hCG regression trends or only pretreatment hCG levels, we can identify precisely (accuracy > 85%), a number of patients as refractory for 8-day methotrexate-folinic acid treatment, among patients diagnosed as low-risk PTD and treated with this regimen. Moreover, the time needed to identify these patients using these weekly cutoff points, was shorter than the time needed by CT scan where 3/15 (20%) of group 2 were diagnosed as being refractory for treatment four weeks after initiating treatment. These findings suggest that the cutoff points of either one or two weeks are useful in identifying chemotherapeutic refractory cases among low-risk PTD patients treated with 8-day methotrexate-folinic acid.

However, these cutoff points may be applicable only to this study population and have to be re-evaluated following larger studies. Moreover, further studies will reveal whether or not the cutoff points at one and two weeks after initiating treatment are really the most useful in identifying chemotherapeutic refractory cases precisely and quickly.

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Address reprint requests to:
T. SHIGEMATSU, M.D.
Department of Obstetrics and Gynecology
Graduate School of Medical Sciences
Kyushu University
Maidashi 3-1-1
Higashi-ku, Fukuoka 812-8582 (Japan)