Methotrexate therapy in trophoblastic disease at the Provincial Taipei Hospital (1955-1966)

A re-evaluation and proposals

CHIEN-TIEN HSU, M.D.
YUNG-SHENG CHENG, M.D.
Taipei, Taiwan, Republic of China

A comparison of survival rate was made between 12 cases of choriocarcinoma treated by hysterectomy and with methotrexate and 20 similar cases without methotrexate therapy. There was no statistically significant difference in end-results. The therapeutic effects of methotrexate on choriocarcinoma as reported in the literature are varying and seem to have been somewhat overestimated. This may be due to enhancement by other anticancer chemicals, too short an observation period, insufficient material, and/or the inclusion of cases of chorioadenoma destruens. Methotrexate unquestionably is beneficial in choriocarcinoma, in view of 5 year survival cases where surgery had failed. A favorable response of central nervous system metastases was observed in this series. It is proposed that therapeutic evaluation of methotrexate be made under uniform and stricter criteria.

SINCE the first report on the promising applicability of methotrexate (MTX) in the treatment of choriocarcinoma by Li, Hertz, and Spencer[25] there have been numerous papers relating to the therapeutic virtues of this drug by investigators in various parts of the world. Based on his equally encouraging results for both choriocarcinoma and chorioadenoma destruens, and with there being no sharp distinction between these entities, Hertz[16] has postulated that the therapeutic effects be discussed under a simple classification, i.e., trophoblastic disease, metastatic and nonmetastatic.

From the Departments of Obstetrics and Gynecology, Provincial Taipei Hospital and Taipei Medical College.

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The glowing optimism has gone so far that there have been sporadic trials with methotrexate at the molar stage for the prophylaxis of choriocarcinoma.[17, 28] Even ignoring the low frequency of choriocarcinoma following an uncomplicated hydatidiform mole, the rationale of this regimen should be proved by such excellence in therapeutic results, such as those in Hertz and associates'[14, 16] series, as to make its value incontrovertible.

At this stage the re-evaluation of the effects of methotrexate as reported in the literature seems necessary before we extend the applicability of this drug. This paper presents our experience in the treatment of trophoblastic disease with methotrexate in Taiwan. Comparison is made with the results reported in the literature, in the hope of gaining further insight into this problem.

Materials and methods

This series consists of 12 cases of choriocarcinoma, 2 cases of chorioadenoma destruens with pulmonary and vaginal metastases, and 2 cases of hydatidiform mole with pul-

Table I. Duration of complete remission in choriocarcinoma cases with and without methotrexate therapy

	No. of patients			
	Methotrexate therapy		*No methotrexate therapy*	
No. of years	*Nonmetastatic*	*Metastatic*	*Nonmetastatic*	*Metastatic*
less than 1		6		13
1-2		1		1
2-3		2		
3-4	1	0	1	
4-5		1		
Over 5		1	3	2
		36.36%		12.5%
Total	12		20	

monary or spinal metastases, which were treated at the Provincial Taipei Hospital from 1955 to 1966. Twenty cases of choriocarcinoma, 34 cases of chorioadenoma destruens, and 170 cases of hydatidiform mole (Table II) treated at the same hospital during the same period without methotrexate were used for comparison. Therefore, in total, 32 cases of choriocarcinoma, 36 cases of chorioadenoma destruens, and 172 cases of hydatidiform mole were included in this paper.

Methotrexate was administered orally to most of the patients in doses of 10 to 25 mg. daily for 5 successive days. Parenteral administration was given in 2 cases. This regimen was repeated at an interval of 1, 2, 3, or 4 weeks, depending on the severity of toxic manifestations. All patients were hospitalized and kept under strict observation with respect to response and toxicity. Chorionic gonadotropin (HCG) determination and radiologic and hematologic examinations were repeatedly performed during and after therapy. Two courses of therapy were added after the HCG titer decreased to less than 50 M.U.

The 9 recent cases of choriocarcinoma treated parenterally with methotrexate were not included in this series in spite of their survival in excellent condition because of too short an observation period.

Results and comments

Tables I and II indicate that when treated with operation alone and without methotrexate therapy the great majority of metastatic choriocarcinoma patients (13 among 16 cases) died within one year and only 2 (12.50 per cent) survived beyond 2 years, while when treated with methotrexate after operation, 36.36 per cent survived beyond 2 years. This seems to indicate the effectiveness of methotrexate on metastatic choriocarcinoma, but we will revert to this point.

Our control cases which were treated by hysterectomy, and, as in Brewer, Smith, and Pratt's series, also with radiation, Nitromin (chlormethine N-oxide), or Sarkomycin (2-methylene-3-oxocyclopentanecarboxylic acid), etc., but without supplemental administration of methotrexate, showed survival rates similar to those in Brewer, Smith, and Pratt's series,[2] as shown in Table III. As will be seen from Tables I and II, regardless of whether or not methotrexate was used, all patients with choriocarcinoma without metastases have survived well beyond 2 years as in Lewis and associates'[24] and Hammond and associates'[11] series, while the great majority of patients with choriocarcinoma with metastases died. The grave influence of metastases on the prognosis of this disease is very evident. This indicates that the therapeutic effects of methotrexate should be evaluated only with the cases of choriocarcinoma with metastases.

Brewer, Smith, and Pratt[2] compared their surgical series with Hertz's series in which methotrexate was administered with or without previous hysterectomy and found that the 48 per cent incidence of complete re-

Table II. Outcome of the patients with trophoblastic disease treated with and without

Pathologic diagnosis	With methotrexate								
	Metastatic			Nonmetastatic			Total		
	No. of cases	No. of survivors	% Survival	No. of cases	No. of survivors	% Survival	No. of cases	No. of survivors	% Survival
Choriocarcinoma	11	4	36.36	1	1	100	12	5	41.66
Chorioadenoma destruens	2	2	100	–	–	–	–	–	100.00
Hydatidiform mole	2	2	100	–	–	–	–	–	100.00

*Seven lost to follow-up, at this moment. These 7 patients were living and well until 1963, when our previous paper was prepared.

Table III. Result of surgical treatment for choriocarcinoma (patients with only dilatation and curettage or exploratory laparotomy were not included)

Author	Metastatic				Nonmetastatic				Total		
	Cases		Survivals		Cases		Survivals		Total cases (No.)	Survivals	
	No.	%	No.	%	No.	%	No.	%		No.	%
Brewer, Smith, and Pratt[2]	52	42.6	10	19.2	70	57.4	29	41.4	122	39	31.9
Present series	11	73.3	2	18.1	4	26.7	4	100	15	6	40.0

Table IV. Survival rate in the cases of metastatic choriocarcinoma treated with or without methotrexate*

Methotrexate	No. of cases	No. of survivors	% Survivals
Yes	11	4	36.36
No	16	2	12.50
Total	27	6	22.22

*$0.157 < p < 0.317$, not significant.

Table V. Survival rate in patients treated by hysterectomy with metastatic choriocarcinoma treated with or without methotrexate*

Methotrexate	No. of cases	No. of survivors	% Survival
Yes	8	2	25.00
No	11	2	18.18
Total	19	4	21.05

*$p > 0.317$, not significant.

mission in the 44 patients with metastatic choriocarcinoma given methotrexate is superior to the 19 per cent cure rate for similar patients in their cases. According to our calculation, the difference between the two series is highly significant ($0.003 < p < 0.05$). However, we must not overlook the fact that Hertz, Lewis, and Lipsett's[14] and Brewer, Smith, and Pratt's[2] series are entirely different in many respects (duration of remission, with or without previous hysterectomy) except for the only common finding, i.e., the presence of metastases.

In our series, as shown in Table IV, there was no significant difference in survival rates between those patients with metastatic choriocarcinoma treated with or without methotrexate, although the former showed an apparently higher survival rate ($0.157 < p < 0.317$).

On the other hand, the diagnosis of choriocarcinoma based only on curettages could result in possible inclusion in one series of cases of chorioadenoma destruens or hydatidiform mole with marked trophoblastic proliferation, as shown in our Cases C. H. F.[20]

methotrexate at the Provincial Taipei Hospital (1955-1966)

Without methotrexate									*Total*		
Metastatic			*Nonmetastatic*			*Total*					
No. of cases	*No. of survivors*	*% Survivors*	*No. of cases*	*No. of survivors*	*% Survival*	*No. of cases*	*No. of survivors*	*% Survival*	*No. of cases*	*No. of survivors*	*% Survival*
16	2	12.50	4	4	100	20	6	30.00	32	11	34.37
15	12	80.00	19	19	100	34	31	91.17	36	33	91.66
10	8	80.00	160	153* (160)	95.62* (100)	170	161*	94.70	172	163	94.70

and C. R. P.[20] This, of course, may result in an unreasonably optimistic evaluation of the therapeutic effect of methotrexate. Since accurate diagnosis of choriocarcinoma in the uterus can be established only by pathologic examination of the removed uterus, assessment of the therapeutic effects of methrotrexate can be more precisely made by comparing the results between those hysterectomized metastatic choriocarcinoma patients who received methotrexate therapy and those who did not receive such therapy. Table V shows that metastatic choriocarcinoma cases treated by hysterectomy followed by methotrexate had higher survival rates than the cases treated by hysterectomy without subsequent methotrexate therapy. The difference, however, is not statistically significant.

These figures are not encouraging, and the cause of the poor results is obscure. It cannot be due to incomplete therapy because we adhered rigidly to continuance of the therapy even after the urinary HCG titer registered below 50 MU. It might be due to the long duration of the tumor before chemotherapy in our cases. Hertz, Lewis, and Lipsett[14] emphasized the duration of the disease process prior to the onset of treatment as the most critical factor in the response to chemotherapy. Chun[5] reported that when choriocarcinoma occurred within 6 months of termination of the antecedent pregnancy, the prognosis was fairly favorable, i.e., only 2 deaths out of 8 cases, while in the 10 cases in which the interval was over 6 months, there were 6 deaths and one relapse. This, however, was not confirmed in our series, i.e., in the former group 4 deaths out of 6 cases and in the latter group 3 deaths out of 6 cases were observed. In this series we selected oral administration primarily and this might play some role because recently we have changed to intramuscular administration and found that the incidence and the severity of toxic manifestations have greatly decreased. Prior hysterectomy or oophorectomy cannot be the cause.[13]

On reviewing the literature, one will see from Table VI that there are optimistic and pessimistic series. The optimistic series represented by Hertz and associates[14, 16] and Bagshawe and McDonald[1] are very important and should be precisely analyzed from every aspect because these should be vital to the determination of the degree of effectiveness of methotrexate. First we must be aware that the encouraging results in their series might have very likely been enforced by vincaleukoblastine (VLB),[14] actinomycin D,[15] and 6-mercaptopurine,[1] as clearly indicated by the comparison of Hertz's three chronologically different series (Table VI). The favorable results are possibly exaggerated by the inclusion of a considerable number of cases under follow-up observation for less than 2 years.

Although most choriocarcinoma patients die within one year, we feel that at least 2 years' observation should be the minimum before considering possible survival, as illustrated by our patient, CC-21, and Douglas' first patient.[8] Suppression of the tumor is

Table VI. Results of methotrexate therapy in choriocarcinoma with metastases from the literature*

Authors	*Choriocarcinoma*			*Related metastatic tumors*		
	Total No. of cases	*No. of complete remissions*	*% Complete remissions*	*Total No. of cases*	*No. of complete remissions*	*% Complete remissoins*
Hertz and associates[13] (1959)	19	3	15.79 (5.05)	8	2	25
Hertz, Lewis; and Lipsett[14] (1956-1961)	44	21	47.7 (?)	19	9	47.3 (?)
Hertz, Holland, and Hreschyshyn[16] (1961-1964)	29	22	76 (?)	21	15	71 (?)
Manahan, Abad, and Lopez[23]	12	5	41.6	3	3	100
Chan[4]	12	5	41.6 (?)			
Chun[5]	18	9	50.0 (?)	6	6	100
Hreshchyshyn, Graham, and Holland[18]	7	2	28.5	3	3	100
Lamb, Morton, and Byron[23] (a)	8	3	37.5	3	1	33.3
Lamb, Morton, and Byron[23] (b)	25	10	40	10	8	80
Bagshawe and McDonald[1]	4(2)	3	75 (0)			
Ishizuka[21]	27	8	29.63 (7.4%)	12	12	100
Mitani[29]	2	0	0	4	2	50
Kobayashi[22]	2	1	50	2	2	100
Douglas[8]	3	1 (2)	33.33 (66.66)			
Hashimoto[12]	3	1	33.33			
Paranjothy[31]	21	7	33.33 (9.5)			
Perlson and Whitsitt[32]	3	2	66.66 (33.33)			
Taylor and Droegemueller[35]	3	1	33.33			
Wei and Ouyang[36]	4	3	75 (0)	3	3	100

*Regardless of the duration of survival, the patients surviving up to the individual reports were included in the number of complete remissions. Nonmetastatic trophoblastic disease included in individual reports was excluded from this table. The figures in parentheses express the corrected rate of survival excluding the cases of no tissue proof or the patients who have been followed for less than 2 years. In Hertz's 1956-1961 series, vincaleukoblastine, in Hertz's 1961-1964 series and in Ishizuka's series (12 cases) actinomycin D, and in Bagshawe's series and in Chun's series (14 cases) 6-mercaptopurine were used in combination with methotrexate. Besides the reports tabulated above, Doniach,[7] Magandie,[26] Hamilton,[10] Freedman, Magagnini, and Glass,[9] and Munford and Haskins[30] reported one case each of complete remission. Munford's patient survived beyond one year and Freedman's patient became pregnant 1½ years after methotrexate therapy. Bucle[3] reported one case of failure and one case under surveillance in an incomplete remission.

Table VI—Cont'd

Authors	Choriocarcinoma			Related metastatic tumors		
	Total No. of cases	*No. of complete remissions*	*% Complete remissions*	*Total No. of cases*	*No. of complete remissions*	*% Complete remissions*
Lewis and associates[24]	4	2	50	4	4	100
Chen and Yeh[6]	12	8	66.6 (25.00)	6	6	100
Present series	11	5	45.45 (36.36)	4	4	100

by no means indicative of ultimate cure. In this regard, the 5 year survival rate of Brewer, Smith, and Pratt[2] and our 3 year survival rate are criteria quite different from the above two series.

In Hertz's 1951 series, where all the diagnoses were based on strict pathologic examination of the removed uteri, as will be seen in Table VI, the therapeutic effects of methotrexate were rather pessimistic. On the other hand, in Hertz's series A[14] and B,[15, 16] where the therapeutic effects were very encouraging, there is no way of knowing how many cases of hysterectomy were included in his choriocarcinoma cases, although allusion was made to 41 cases of hysterectomy among 63 cases of metastatic trophoblastic disease but no distinction was made between choriocarcinoma and chorioadenoma destruens.

It is widely believed by clinicians and pathologists that chorioadenoma destruens and choriocarcinoma are prognostically entirely different entities. Spontaneous regression of chorioadenoma destruens has not infrequently been reported in the literature and also observed in our cases.[20] Even without methotrexate therapy the mortality rate in chorioadenoma destruens is as low as in hydatidiform mole, regardless of the presence or absence of metastases in both entities in our series (Table II). This also accounts for the absolutely beneficial results with methotrexate therapy (nearly 100 per cent survival) in chorioadenoma destruens in the literature (Table VI), with the exception of Hertz's series,[13, 14, 16] in which the mortality rate in the chorioadenoma destruens cases treated with methotrexate is higher than that in our cases without methotrexate therapy. The explanation for this is not apparent.

From the foregoing it will be seen that until the degree of effectiveness of methotrexate in choricarcinoma is definitely determined, choriocarcinoma and chorioadenoma destruens, the two prognostically different entities, should be observed separately in determining the effectiveness of methotrexate. Evaluation of the drug should be based on strict pathologic study of hysterectomized uteri, establishing the correct diagnosis prior to the onset of methotrexate therapy. This means primary use of methotrexate for trophoblastic disease should be restricted only to cases where further childbearing is desired or to the cases of poor operative risk.

The therapeutic effects of methotrexate in choriocarcinoma reported in the literature vary considerably. They should be carefully re-evaluated under strict and uniform criteria, i.e., precise diagnosis by pathologic examination of hysterectomy and hysterotomy specimens, presence or absence of metastases, approximately the same size of material, and the same standard of determining possible survival (for instance, 2 or 3 years of complete remission), etc.

In our series an apparent but not statistically significant improvement in survival rate was observed with the administration of methotrexate for metastatic choriocarcinoma as compared with surgical treatment.

However, the over-all therapeutic effectiveness of methotrexate in the individual reports, though variable, and the dramatic cure in individual cases of choriocarcinoma, particularly in instances where surgery has failed, convince us of the usefulness of this drug in the treatment of choriocarcinoma. Nevertheless, careful analyses of Hertz's and Bagshawe's results and the results in our series. (coupled with our recent unpublished data) suggest that the encouraging results in the literature were obtained by the combination of methotrexate and other anticancer drugs but not with methotrexate alone.

Normal pregnancy following methotrexate therapy has been reported by some authors.[9, 15] In this series, there was a case of mild malformation (polydactylism) of a baby girl who was born to a mother who had been treated with methotrexate for metastatic hydatidiform mole 5 months prior to the pregnancy. On the other hand, also in this series, a patient with choriocarcinoma who had been treated with methotrexate gave birth to a normal healthy full-term baby girl 2½ years after the therapy.

Mention should also be made of those cases in this series in which metastases to the central nervous system were very suggestive (CC-18, CC-26, CC-28, CC-29) and treatment with methotrexate produced excellent effects. This is in contrast with the pessimistic results in the literature.

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