Dose-Related Increases in Cerebrospinal Fluid Concentrations of Methotrexate in a Postoperative Patient with Glioblastoma

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OBJECTIVE: To investigate the postoperative pharmacokinetics of methotrexate in the plasma and cerebrospinal fluid (CSF) in the space created by tumor removal of a patient with glioblastoma during hyperosmotic disruption of the blood–brain barrier (BBB) and intraarterial chemotherapy with a stepwise increase in the methotrexate dosage.

CASE SUMMARY: A 30-year-old Japanese woman with glioblastoma received four courses of hyperosmotic disruption of the BBB and intraarterial chemotherapy with a combination of peplomycin, vindesine, nimustine, pirarubicin, and methotrexate. The patient was initially administered mannitol; anticancer drugs were then infused into the left internal carotid artery. Following the first, second, third, and fourth courses of treatment, methotrexate 350, 700, 1000, and 1500 mg, respectively, were administered for 30 minutes. Samples of blood and CSF from the space created by tumor removal were obtained. Methotrexate concentrations were measured by fluorescence polarization immunoassay and the pharmacokinetic parameters of methotrexate in plasma and CSF were estimated.

RESULTS: The plasma concentration of methotrexate peaked at the end of drug infusion, then decreased in a biexponential decay manner during the remainder of the treatment period. The CSF concentration of methotrexate in the space created by tumor removal peaked two hours after drug administration, then monoexponentially decreased. Although the maximal CSF concentration of methotrexate in the space created by tumor removal was lower than that in the plasma, the CSF concentration of methotrexate in the space created by tumor removal exceeded that in the plasma six hours after drug infusion. The half-life of methotrexate in the CSF exceeded that in the plasma. The AUC for the plasma and CSF methotrexate concentration increased parallel with the methotrexate dosage. The mean CSF AUC of methotrexate was 59.4% of that found in plasma.

CONCLUSIONS: The CSF AUC of methotrexate in the space created by tumor removal increased parallel with the methotrexate dosage during hyperosmotic disruption of the BBB and intraarterial chemotherapy.

KEY WORDS: methotrexate, pharmacokinetics, cerebrospinal fluid, intraarterial chemotherapy.

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The blood–brain barrier (BBB) can impair the delivery of chemotherapeutic agents, even in the presence of high systemic blood concentrations. Hyperosmotic disruption of the BBB and the intraarterial administration of methotrexate and other chemotherapeutic agents have been applied to patients with brain tumors in an attempt to increase the amount of drug that reaches the tumor and surrounding brain tissue.[1,2] Cosolo et al.[3,4] reported that hyperosmotic disruption of the BBB with mannitol increased the intracerebral concentrations of methotrexate in rats that received intraarterial doses of this drug. Williams et al.[5] reported that 12 patients with supratentorial glioma who underwent hyperosmotic disruption of the BBB and combination chemotherapy with intraarterial methotrexate, intravenous cyclophosphamide, and oral procarbazine prior to radiotherapy, as well as four of 10 patients with enlarged tumor, showed a radiographic tumor response, defined as a 50% reduction in tumor volume. However, the pharmacokinetics of intraarterially administered chemotherapeutic agents in the space created by tumor removal have not been investigated in detail. In a previous report[6] we described the pharmacokinetics of methotrexate in the cerebrospinal fluid (CSF) of the ventricle and in the space created by tumor removal during hyperosmotic disruption of the BBB and intraarterial combination chemotherapy in a postoperative patient with glioblastoma. We found that the concentration of methotrexate in the CSF occupying the space created by tumor removal always exceeded that in the ventricle. In our current report, we describe the pharmacokinetics of methotrexate in the plasma and in the CSF occupying the space created by tumor removal in a patient with glioblastoma who underwent hyperosmotic disruption of the BBB and intraarterial combination chemotherapy with a stepwise increase in the methotrexate dosage.

PATIENT AND METHODS

A 30-year-old Japanese woman (50 kg, body surface area 1.47 m²) underwent surgery to remove most of a glioblastoma (95%),

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followed by radiation therapy. We expected that the BBB in the space created by tumor removal would be locally destroyed by surgery; however, the BBB of the artery of brain tissue surrounding the space created by tumor removal was maintained. Thereafter, she gave written informed consent to receive four courses of hyperosmotic disruption of the BBB with the hyperosmolar agent mannitol and intraarterial combination chemotherapy at intervals of four to five weeks. Chemotherapy consisted of peplomycin, vindesine, nimustine, pirarubicin, and methotrexate. These drugs were diluted in NaCl 0.9% for injection and administered via the left internal carotid artery. During the first course of treatment, the patient sequentially received 20% mannitol 50 mL over five minutes, then infusions of peplomycin 10 mg over 10 minutes, vindesine 2 mg over 10 minutes, nimustine 50 mg over five minutes, methotrexate 350 mg over 30 minutes, and methylprednisolone 80 mg over five minutes. During the second course of treatment, 20% mannitol 50 mL over five minutes was followed by infusions of vindesine 3 mg over 10 minutes, pirarubicin 30 mg over 10 minutes, methotrexate 700 mg over 30 minutes, and methylprednisolone 80 mg over five minutes. The third course of treatment consisted of 20% mannitol 50 mL over five minutes, followed by nimustine 50 mg over five minutes, pirarubicin 45 mg over 15 minutes, methotrexate 1000 mg over 30 minutes, and methylprednisolone 80 mg over five minutes. The last course of treatment consisted of 20% mannitol 50 mL over five minutes, followed by nimustine 50 mg over five minutes, pirarubicin 45 mg over 10 minutes, methotrexate 1500 mg over 30 minutes, and methylprednisolone 80 mg over five minutes. During all courses of treatment, the patient also received leucovorin 15 mg orally or intravenously every six hours for six treatments, beginning six hours after methotrexate administration. The patient's clinical response to treatment was partial, and the decrease of the wall size of the space created by tumor removal was observed according to magnetic resonance imaging. No complications were observed during the treatment. The patient was discharged four weeks after the last treatment.

Prior to drug administration, an Ommaya reservoir was placed in the space created by tumor removal to sample CSF. Samples of plasma and CSF were obtained before and 0.5, 1.5, 3.5, 6, 18, 24, 48, and 72 hours after the methotrexate infusion. Blood samples were immediately drawn into heparinized tubes, centrifuged, and stored at –40 °C. CSF samples were immediately frozen and stored at –40 °C. Plasma and CSF samples were assayed within one week.

The plasma and CSF concentrations of methotrexate were measured by fluorescence polarization immunoassay (TDx, Abbott Laboratories, North Chicago, IL). In this method, 10 µL of plasma and CSF samples were used and these samples diluted 300 times with the buffer solution. Thus, we used the calibration curve of plasma for the measurement of methotrexate concentration in the CSF. The detection limit of methotrexate was 0.009 µg/mL. This method was highly specific and only minimally (<1%) cross-reactive with the major metabolite of methotrexate, 7-hydroxymethotrexate.[7] The within- and between-day coefficients of variation were <5%.

The pharmacokinetic parameters of methotrexate in plasma and CSF were estimated using a modified computer program (MULTI)[8] with the following equation:

$$Cp = A \cdot (\exp(-\alpha \cdot t) - \exp(-\alpha \cdot (t - t_1))) + B \cdot (\exp(-\beta \cdot t) - \exp(-\beta \cdot (t - t_1))), \quad (t \geq t_1)$$

$$C_{CSF} = C \cdot (\exp(-ke \cdot t) - \exp(-ka \cdot t)).$$

where Cp is the plasma concentration, C_{CSF} is the CSF concentration in the space created by tumor removal, t_1 is the infusion time, α is the elimination rate constant of the first decay phase in the plasma, β is the elimination rate constant of the second decay phase in the plasma, ka is the distribution rate constant to the space created by tumor removal, and ke is the CSF elimination rate constant from the space created by tumor removal. A and B are the biexponential equation constants, and C is the monoexponential equation constant.

Results

The plasma and CSF concentrations of methotrexate during all courses of treatment are shown in Figures 1 and 2. The plasma concentration of methotrexate peaked at the end of infusion, then decayed biexponentially during the remainder of all courses of treatment. The CSF concentration of methotrexate in the space created by tumor removal peaked two hours after drug administration, then was eliminated monoexponentially. Although the maximal concentrations of methotrexate in the CSF were lower than that in the plasma, the former exceeded that in the latter six hours after infusion during all courses of treatment.

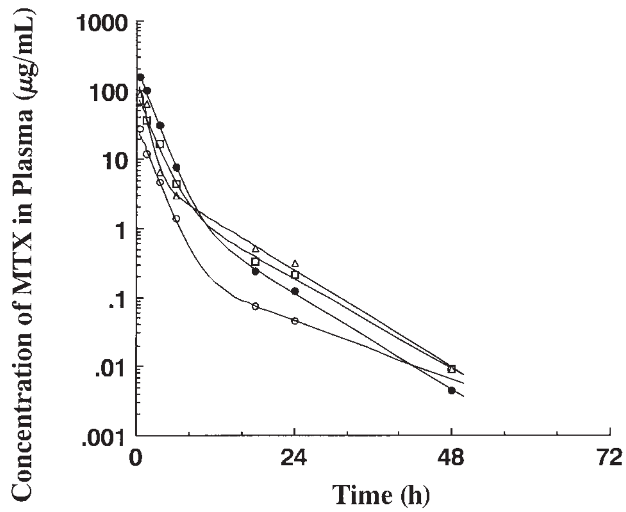

Figure 1. Plasma concentrations of methotrexate (MTX) after four courses of hyperosmotic disruption of the blood–brain barrier and intraarterial chemotherapy. First (○), second (□), third (△), and fourth (●) course of treatment (MTX 350, 700, 1000, and 1500 mg, respectively).

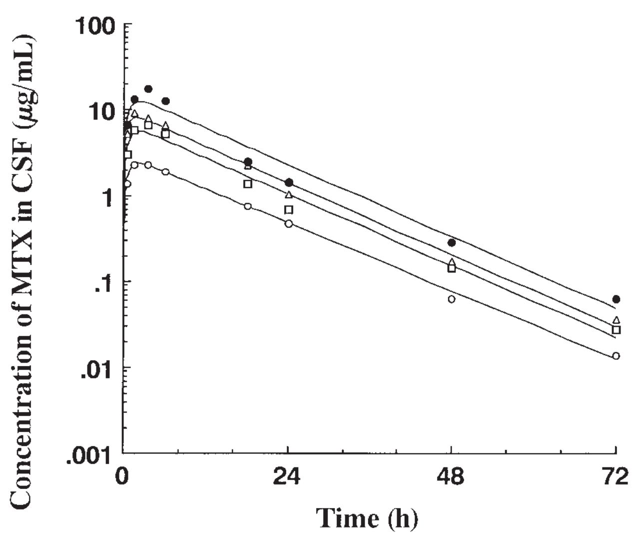

Figure 2. Concentrations of methotrexate (MTX) in cerebrospinal fluid occupying the space created by tumor removal after four courses of hyperosmotic disruption of the blood–brain barrier and intraarterial chemotherapy. First (○), second (□), third (△), and fourth (●) course of treatment (MTX 350, 700, 1000, and 1500 mg, respectively).

The pharmacokinetic parameters of methotrexate in plasma and in the CSF occupying the space created by tumor removal are shown in Table 1. The mean half-lives of methotrexate in the first ($t_{1/2\alpha}$) and second ($t_{1/2\beta}$) decay phases in plasma were 1.09 ± 0.29 and 6.15 ± 1.66 hours (mean ± SD), respectively, according to the two-compartment model. The mean half-life of methotrexate in CSF occupying the space created by tumor removal (8.77 ± 0.24 h) exceeded that in the plasma. When the dosage of methotrexate was increased stepwise, the AUC of methotrexate in the plasma and CSF increased in parallel (Figure 3). The dosage of methotrexate (X) and plasma AUC was positively correlated (Y = 0.214 X : r^2 = 0.986), as was the dosage of methotrexate and CSF (Y = 0.121 X : r^2 = 0.998). The mean CSF AUC of methotrexate in the space created by tumor removal was 59.4 ± 8.1% of that of the plasma.

Discussion

In patients with brain tumors, anticancer drugs have been administered intraarterially in efforts to increase their concentration at the tumor site.[3] Pharmacologic studies of normal and tumor-bearing rodents and dogs, as well as the extrapolated clinical data, have shown that modification of the BBB increases drug concentrations in the tumor and in parts of the brain supplied by the infused artery.[1,2,9] Hyperosmotic disruption of the BBB also increases the concentration of anticancer drugs in brain tumors. For example, Cosolo and Christophidis[3] reported that hyperosmotic disruption of the BBB with the hyperosmolar agent mannitol increased intracerebral concentrations of methotrexate in rats with readily transplantable intracerebral osteogenic sarcomas. They also reported that when adult rats were infused with methotrexate with or without mannitol via the internal carotid artery, the methotrexate concentration on the side infused with mannitol was four to five times that of the noninfused hemisphere.[4] Williams et al.[5] reported that 12 patients with supratentorial glioma who underwent hyperosmotic disruption of the BBB and combination chemotherapy with intraarterial methotrexate, intravenous cyclophosphamide, and oral procarbazine prior to radiotherapy, as well as four of 10 patients with enlarged tumor, showed a radiographic tumor response, defined as a 50% reduction in tumor volume. Hayashi and Kyuma[10] described six patients with nimustine-resistant, recurrent gliomas who received hyperosmotic disruption of the BBB and high doses of intraarterially infused methotrexate (1000–2000 mg/artery). Of the six patients, one exhibited a complete response on the computed tomography and one showed intratumoral necrosis.

It is generally accepted that the concentration of anticancer drugs in the CSF reflects that found in the brain. Since the BBB impairs the delivery of anticancer drugs to the brain, even at high systemic blood concentrations, the intravenous administration of methotrexate results in a CSF concentration of the drug that is 2–5% of the plasma concentration.[11,12] In our patient, the maximal CSF concentration of methotrexate in the space created by tumor removal was lower than that in plasma (8.6–11.3% of the plasma concentration). However, the CSF concentration of methotrexate in the space created by tumor removal ex-

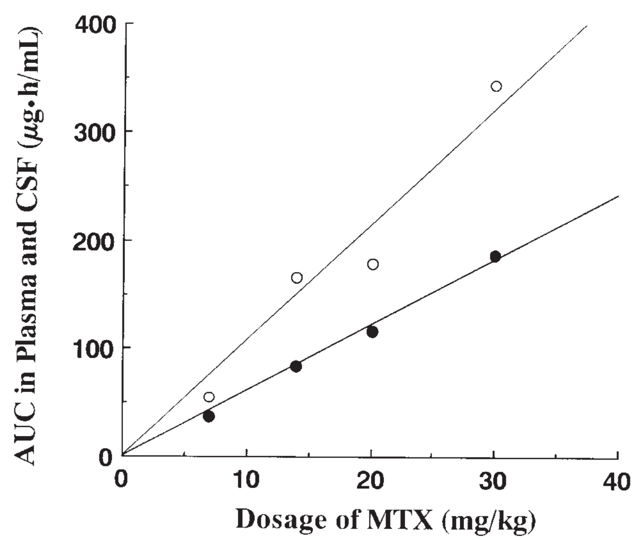

Figure 3. Relationship between dosage and the AUC of methotrexate (MTX) in plasma and cerebrospinal fluid (CSF) occupying the space created by tumor removal. Plasma (○) and CSF (●).

Table 1. Pharmacokinetic Parameter Values of Methotrexate in Plasma and in CSF Occupying the Space Created by Tumor Removal after Hyperosmotic Disruption of the BBB and Intraarterial Chemotherapy

Treatment	Dosage (mg)	Cp_{max} (μg/mL)	$C_{CSF/max}$ (μg/mL)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2CSF}$ (h)	AUC_{plasma} (μg•h/mL)	AUC_{CSF} (μg•h/mL)	Ratio (AUC_{CSF} /AUC_{plasma})
1	350	27.00	2.32	1.27	8.62	9.13	54.11	36.71	0.678
2	700	70.61	6.64	1.24	5.62	8.68	165.03	83.92	0.509
3	1000	85.62	9.00	0.656	5.15	8.62	177.66	115.25	0.649
4	1500	150.82	17.04	1.21	5.21	8.63	343.96	186.76	0.543
mean ± SD				1.09 ± 0.29	6.15 ± 1.66	8.77 ± 0.24			0.594 ± 0.081

AUC_{CSF} = AUC of CSF occupying the space created by tumor removal; AUC_{plasma} = AUC of plasma; BBB = blood–brain barrier; $C_{CSF/max}$ = maximum concentration of methotrexate in CSF occupying the space created by tumor removal; Cp_{max} = maximum concentration of methotrexate in plasma; CSF = cerebrospinal fluid; $t_{1/2\alpha}$ = half-life of methotrexate in plasma of first-phase decay (= ln 2/α); $t_{1/2\beta}$ = half-life of methotrexate in plasma of second-phase decay (= ln 2/β); $t_{1/2CSF}$ = half-life of methotrexate in CSF occupying the space created by tumor removal (= ln 2/ke).

ceeded that in the plasma at six hours after drug infusion. We previously reported that the plasma methotrexate concentration profiles obeyed a two-compartment model and CSF methotrexate concentration profiles obeyed a one-compartment model.[6] In our patient, there is a possibility that the data of CSF concentrations from 12–24 hours were overestimated and the data from 48–72 hours were underestimated. However, we were unable to obtain many of the samples of CSF needed to plot the results. Thus in this case study, we thought that the CSF methotrexate concentration profiles fundamentally obeyed a one-compartment model. Consequently, we found that the CSF AUC of methotrexate in the space created by tumor removal increased in a parallel manner when the methotrexate dosage was increased step by step. The mean CSF AUC of methotrexate in the space created by tumor removal was 59.4% of plasma. However, the half-life of methotrexate in the CSF did not differ significantly during any of the courses of treatment.

The CSF AUC of methotrexate was very high for the space created by tumor removal, while the AUC values of methotrexate for the ventricle were consistent with the 2–5% values during the intravenous administration of methotrexate that have been reported by others.[11,12] Furthermore, in a previously reported case,[6] we determined that the CSF AUCs in the ventricle and the space created by tumor removal were 3.5% and 148.2% of plasma, respectively, during the hyperosmotic disruption of the BBB and intraarterial administration of a total dose of methotrexate 1000 mg, in which two courses of methotrexate 500 mg were each infused for 30 minutes via the right internal carotid and vertebral arteries, respectively. In that patient, we found a nonlinear response with high-dose administration of methotrexate (>1000 mg/artery). However, in the present patient, we found a linear response with low-dose administration (<1500 mg/artery). We had expected the maximum limiting dose of methotrexate to obey the linear response rule from 1000 to 2000 mg/artery.

Those findings of a linear response could be explained by the prolonged half-life of methotrexate in the space created by tumor removal as compared with the plasma or ventricular space. In addition, we surmised that the methotrexate concentration in the space created by tumor removal remained elevated after the methotrexate was administered according to the following process. First, the methotrexate administered by hyperosmotic disruption of the BBB and intraarterial chemotherapy was delivered to the space created by tumor removal. We had assumed that the BBB in the space created by tumor removal was locally destroyed by prior surgery and that the passive transport of methotrexate within the injured area was increased compared with that of the normal brain. Thus, the methotrexate concentration at the site reflected the dose of methotrexate administered that had accumulated in the space because it was enclosed by surrounding brain tissue. The methotrexate was then eliminated slowly by passive transport to the surrounding brain cells, where it was metabolized. We thought that the same concept would be applicable to our patient.

The present case is the first to measure the concentration of methotrexate in the space created by tumor removal when the methotrexate dosage is increased in a stepwise manner. The CSF AUCs of methotrexate in the space created by tumor removal increased parallel with the methotrexate dosage when administered via the same infusion time and route. Although these findings require confirmation in a larger patient population, our results may be useful in guiding intraarterial dosing of methotrexate during hyperosmotic disruption of the BBB and intraarterial combination chemotherapy for patients with glioblastoma.

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EXTRACTO

OBJETIVO: Investigar la farmacocinética de metotrexato en el plasma y en el líquido cefalorraquídeo luego de remoción quirúrgica de un tumor a un paciente con glioblastoma.

RESUMEN DEL CASO: Una mujer japonesa de 30 años con glioblastoma recibió cuatro cursos de quimioterapia intra-arterial con una combinación de peplomicina, vindesina, nimustina, pirarubicina, y metotrexato luego de ruptura de la barrera hematoencefálica por hiperosmolaridad con manitol. La quimioterapia fue administrada mediante infusión a la arteria carótida interna izquierda. El paciente recibió 350, 700, 1000, y 1500 mg de metotrexato al final del primer, segundo, tercer, y cuarto curso de quimioterapia, respectivamente. Se tomaron muestras del líquido cefalorraquídeo en el espacio creado al remover el tumor. Las concentraciones de metotrexato fueron medidas mediante inmuno ensayo de fluorescencia polarizada y se estimaron los parámetros farmacocinéticos de este fármaco en el plasma y en el líquido cefalorraquídeo.

RESULTADOS: La concentración de metotrexato en el plasma llegó a un máximo al final de la infusión y disminuyó de manera bi-exponencial durante el resto del período de tratamiento. La concentración de metotrexato llegó a un máximo en el líquido cefalorraquídeo en el espacio creado al remover el tumor luego de dos horas y disminuyó mono-exponencialmente. A pesar de que las concentraciones máximas de metotrexato en el líquido cefalorraquídeo en el espacio creado al remover el tumor eran más bajas que en el plasma, seis horas luego de la infusión la concentración del fármaco en el líquido cefalorraquídeo excedía la del plasma. La vida media de metotrexato en el líquido cefalorraquídeo excedió la del plasma. El área debajo de la curva de metotrexato en el líquido cefalorraquídeo y el plasma aumentaron paralelamente con la dosis de metotrexato. El promedio del área debajo de la curva de metotrexato en el líquido cefalorraquídeo era 59.4% de la del plasma.

CONCLUSIONES: El área debajo la curva de metotrexato en el líquido cefalorraquídeo aumentó paralelamente con la dosis de metotrexato durante la ruptura de la barrera hematoencefálica por hiperosmolaridad y la administración de quimioterapia intra-arterial.

LESBIA HERNÁNDEZ

RÉSUMÉ

OBJECTIF: Etudier la pharmacocinétique du méthotrexate (MTX) dans le plasma et le liquide céphalo-rachidien (LCR) dans l'espace créé par la résection d'un glioblastome. Cette étude s'effectue durant la rupture hyperosmotique de la barrière hémato-encéphalique (HODBBB) et l'administration de chimiothérapie intra-artérielle avec une augmentation par paliers de la dose de MTX.

RÉSUMÉ DU CAS: Une japonaise de trente ans atteint d'un glioblastome a reçu quatre cycles de HODBBB et de chimiothérapie intra-artérielle comprenant une combinaison de peplomycine, vindésine, nimustine, pirarubicine, et de méthotrexate. Le patiente a d'abord reçu du mannitol puis les antinéoplasiques ont été administrés dans l'artère carotide interne gauche. Durant les premier, deuxième, troisième, et quatrième cycles de chimiothérapie, elle a reçu 350, 700, 1000, et 1500 mg de MTX, respectivement, sur une période de 30 minutes. Des échantillons sanguins et du LCR ont été prélevés dans l'espace créé par la résection de la tumeur. Les concentrations de MTX ont été mesurées par immunofluorescence polarisée et les paramètres pharmacocinétiques du MTX dans le plasma et le LCR ont ainsi pu être estimés.

RÉSULTATS: La concentration plasmatique maximale (Cpmax) du MTX a été atteinte à la fin de la perfusion, puis elle a diminué de façon bi-exponentielle durant le reste de la période de traitement. La concentration de MTX du LCR dans l'espace créé par la résection de la tumeur a atteint sa Cpmax deux heures après l'administration, puis a diminué de façon mono-exponentielle. Bien que la concentration de MTX dans le LCR soit inférieure à celle du plasma, celle du MTX dans l'espace créé par la résection de la tumeur a surpassé celle du plasma six heures après la perfusion. La demi-vie du MTX dans le LCR dépassait celle du plasma. La surface sous la courbe de la concentration plasmatique en fonction du temps et la concentration de MTX dans le LCR ont augmenté parallèlement à l'augmentation du dosage de MTX. La surface sous la courbe moyenne du MTX dans le LCR a été de 59.4% de celle trouvée dans le plasma.

CONCLUSIONS: Les surfaces sous la courbe du MTX dans l'espace créé par la résection de la tumeur ont augmenté parallèlement au dosage croissant du MTX durant l'HODBBB et la chimiothérapie intra-artérielle.

LOUISE GAGNON