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STUDY OF THE EFFECT OF LOMUSTIN ON HER2-POSITIVE BREAST CANCER IN FVB/N HER-2 TRANSGENIC MICE

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Abstract

Because of the high risk of brain metastases from HER2-positive breast cancer, the study of the anticancer activity of drugs used to treat brain tumors, in particular lomustine, is of great importance. In the FVB/N Her-2 transgenic mice bearing HER2-positive breast cancer (BC HER2+), a single oral administration of lomustine at a dose of 50 mg/kg resulted in a significant tumor growth inhibition (up to 96 %, $p < 0.0001$). The tumor growth index (TGI) expressed as a ratio between the areas under the kinetic curves of tumor growth in the study and control groups and amounted to 33 % ($p < 0.001$) indicated the high activity of lomustine. However, the effect of lomustine on intramuscularly transplanted Ehrlich tumor was insignificant (tumor growth inhibition and tumor growth index were ≤ 39 % and 68 %, respectively). Lomustine administered orally at a single dose of 50 mg/kg 24 hours after intracranial transplantation of BC HER2+ increased the median survival time up to 30 days in FVB/N mice compared to 21 days in the control group mice ($p < 0.001$). The high therapeutic effect of lomustine in HER2-positive breast cancer mice is likely can be explained by the biological characteristics of this tumor; therefore clinical trials of lomustine for HER2-positive tumors are needed.

Key words: HER2-positive breast cancer, HER2 transgenic FVB/N mice, lomustine, intracranial tumor, tumor growth index.

ИЗУЧЕНИЕ АКТИВНОСТИ ЛОМУСТИНА ПРИ ПРЕВИВАЕМОМ HER2-ПОЛОЖИТЕЛЬНОМ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ У МЫШЕЙ ЛИНИИ FVB/N, ТРАНСГЕННЫХ ПО HER2

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Аннотация

В связи с высоким риском метастазирования HER2-положительного рака молочной железы в головной мозг целесообразно изучение активности при HER2-положительных опухолях препаратов, используемых в терапии опухолевого поражения головного мозга, в частности ломустина. У мышей линии FVB/N, трансгенной по гену рецептора эпидермального фактора роста 2-го типа (HER2), с трансплантированным внутримышечно сингенным HER2-положительным раком молочной железы (PMЖ HER2+) однократное пероральное введение ломустина в дозе 50 мг/кг вызвало значительное торможение роста опухоли (ТРО=96 %; $p<0,0001$). О высокой активности ломустина при этой опухоли свидетельствовал и индекс роста опухоли (ИРО), выражающий процентное соотношение между площадью под кинетической кривой роста опухоли в исследуемой и контрольной группах и составивший 33 % ($p<0,001$). В то же время на перевитой внутримышечно опухоли Эрлиха эффект ломустина был незначительным (ТРО $\leq$ 39 %, ИРО=68 %). Ломустин при однократном пероральном введении в дозе 50 мг/кг через 24 ч после интракраниальной трансплантации PMЖ HER2+ мышам FVB/N увеличил медиану продолжительности их жизни до 30 дней по сравнению с 21 днем в контроле ($p<0,001$). Высокий терапевтический эффект ломустина при HER2-положительном раке молочной железы у мышей, вероятно, объясняется биологическими особенностями этой опухоли и позволяет считать целесообразным клиническое изучение ломустина при HER2-положительных новообразованиях.

Ключевые слова: HER2-положительный рак молочной железы, трансгенные по гену HER2 мыши линии FVB/N, интракраниальная опухоль, ломустин, индекс роста опухоли.

Introduction

Human epidermal growth factor receptor 2 (HER2 receptor) is a member of the epidermal growth factor receptor family encoded by the ERBB2 (HER2) proto-oncogene. HER2 overexpression is determined in 25–30 % of patients with breast cancer and is associated with an aggressive course of the disease, low sensitivity to chemotherapy and hormonal therapy [1]. In addition to breast cancer, HER2 overexpression is observed in cells of gastric cancer, colorectal cancer, pancreatic cancer, salivary cancer, mucinous and clear-cell ovarian cancer, and endometrial cancer [2, 3].

In HER2-positive metastatic breast cancer patients, the incidence of central nervous system (CNS) metastases is very high, 30–55 % [4], an incidence that is considerably higher than that reported for breast cancer overall (5–15 %) [5]. HER2-positive breast

cancer patients with CNS metastases treated with trastuzumab emtanzine had longer overall survival than patients treated with combination of lapatinib and capecitabine (median 26.8 months compared to 12.9 months); however, survival of patients without disease progression was equally low (5.9 and 5.7 months, respectively) [6]. Lomustine is a chemotherapy drug used to treat brain tumors. Because of the high risk of brain metastasis from HER2-positive breast cancer, we aimed to study the effect of lomustine on HER2-positive tumors.

Material and Methods

FVB/N Her-2 transgenic mice and BALB/c mice were used in the study. FVB/N mice carrying the HER2 oncogene were originally obtained from the National Institute of Aging (Ancona, Italy) and bred in our

animal facilities. These mice are characterized by a significant frequency of development of spontaneous mammary tumors in females, sometimes they also occur in males [7, 8].

The animals were kept under standard conditions (12:12 h light:dark artificial lighting regimen at 20–25 °C by HVAC system) and had free access to standard food and tap water ad libitum. All experimental studies were carried out in accordance with the rules adopted by the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (Strasbourg, 1986), under the supervision of the ethical committee of the N.N. Petrov National Medical Research Center of Oncology.

To obtain an experimental therapeutic model of transplantable HER2-positive breast cancer, a mammary tumor arising spontaneously in the FVB/N Her-2 transgenic mouse was inoculated to 9 other healthy male mice of the same strain. Mice were inoculated intramuscularly into the femoral muscle with 0.2 ml of a 20 % tumor cell suspension diluted with 0.9 % sodium chloride solution. On day 31 after inoculation, the average weight of tumor nodules was 2463 ± 153 mg. Histological examination revealed invasive breast cancer (Fig. 1). A real-time PCR and delta Ct method detected a pronounced increase in HER2 expression. Cryopreserved tumour tissue is stored in the tumor bank of the N.N. Petrov National Medical Research Center of Oncology.

The effect of lomustine on the growth of HER2+ breast tumor was studied after its extra- and intracranial transplantation. Extracranial transplantation of HER2+ breast cancer was performed by intramuscular

injection into the thigh muscle of 0.2 ml of 20 % tumor cell suspension diluted with 0.9 % sodium chloride solution. On day 6 after transplantation, 14 of the 28 mice were given an oral dose of 50 mg/kg lomustine as a suspension in a 2.5 % starch solution in a volume of 0.2 ml per 10 g of mouse body weight. The control group included the other 14 mice. They were administered with a 2.5 % starch solution of 0.2 ml per 10 g of body weight.

The effect of lomustine on HER2+ breast cancer in FVB/N mice was compared to that on a solid Ehrlich tumor in BALB/c mice. Ehrlich tumor was transplanted intramuscularly to 20 male BALB/c mice by injecting into the thigh muscle with 0.2 ml of 0.9 % sodium chloride solution containing 5×10^6 tumor cells collected from ascitic fluid of a mouse with Ehrlich ascites tumor. On day 6 after inoculation of Ehrlich tumor, 10 mice were administered with lomustine once orally at a dose of 50 mg/kg as a suspension in a 2.5 % starch solution. The other 10 mice served as controls and were treated with a 2.5 % starch solution.

Intracranial transplantation of HER2+ breast cancer was performed by injecting into the brain of 0.025 ml of 20 % tumor suspension according to the modified method of intracerebral infection of mice with rabies virus [9]. Histological examination revealed brain tumor growth (Fig. 2). The study included 22 FVB/N Her-2 transgenic male mice. Twenty-four hours after inoculation, 10 mice were given lomustine at a dose of 50 mg/kg once orally in a 2.5 % starch solution, and 12 mice of the control group were orally administered with a 2.5 % starch solution.

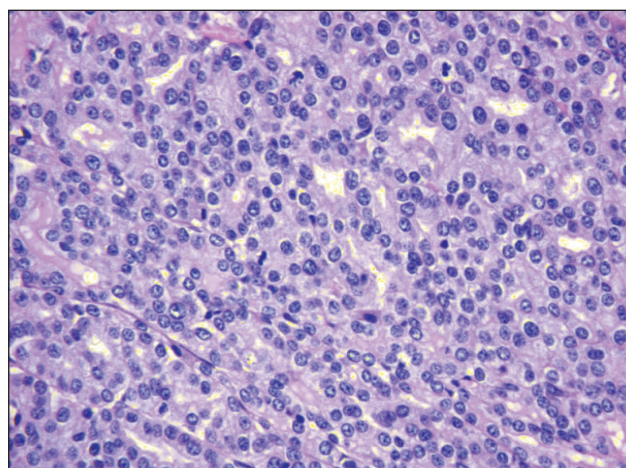


Fig. 1. Histological microphotograph of intramuscularly transplanted HER2-positive invasive breast cancer in an FVB/N mouse. Hematoxylin and eosin. $\times 400$

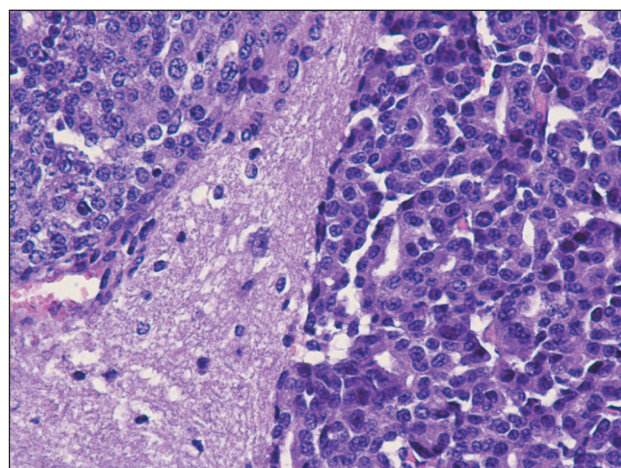


Fig. 2. Histological microphotograph of the mouse FVB/N brain with a transplanted intracranially HER2-positive invasive breast cancer. Hematoxylin and eosin. $\times 400$

The antitumor activity of intramuscularly transplanted tumors was assessed by the tumor growth inhibition (TGI), area under the tumor growth kinetic curve (S) and tumor growth index (TGI) [10]. Tumor growth inhibition (TGI) was calculated using the formula

$$TGI = \frac{V_C - V_T}{V_C} \times 100,$$

where TGI is a tumor growth inhibition (%); V_C is a mean tumor volume in mice in the control group, mm^3 ; V_T is a mean tumor volume in treated mice, mm^3 .

Tumor growth index (TGI) was calculated using the formula

$$TGI = \frac{S_T}{S_C} \times 100,$$

where TGI is a tumor growth inhibition (%); S_T is an area under the tumor growth kinetic curve in treated

mice group, S_C is an area under the tumor growth kinetic curve in the control group.

In mice with HER2+ breast cancer transplanted intracranially, the therapeutic effect was estimated by the median survival time (MST) and by the increase in survival time (IST)

$$IST = \frac{MST_T - MST_C}{MST_C} \times 100,$$

where MST_T is the median survival time in the treated mice group, MST_C is the median survival time in the control group

The statistical data analysis was performed using the methods of variation statistics with the statistical software packages SPSS Statistics 17.0 and GraphPad Prism 6.0. The significance of differences was assessed using the Student's t-test, Fisher's LSD test for one-way ANOVA, Mantel-Haenszel test.

Table 1

The effect of lomustine on the growth of an intramuscularly grafted HER2-positive invasive breast cancer (BC HER2+)

Group	Tumor volume mm ³ (M±m), TI (%), p vs control					S	TGI
	Day after transplantation						
	12	16	20	24	28		
I .Control (n=14)	495 ± 91	1375 ± 198	2251 ± 262	3612 ± 381	6339 ± 455	50286 ± 4456	100 %
II. Lomustine 50 mg/kg (n=14)	19 ± 7 96 % p=0.0004	291 ± 80 75 % p<0.0001	795 ± 156 67 % p<0.0001	1499 ± 250 58 % p<0.0001	3055 ± 358 52 % p<0.0001	16488 ± 2607 p<0.001	33 % p<0.001

TI (%) – tumor growth inhibition, S – area under the tumor growth kinetic curve, TGI – tumor growth index (which is the ratio of S in the study group to S in the control group, expressed as a percentage).

Table 2

The effect of lomustine on the growth of an intramuscularly grafted Ehrlich tumor

Group	Tumor volume mm ³ (M±m), TI (%), p vs control					S	TGI
	Day after transplantation						
	10	12	15	17	20		
I .Control (n=12)	2119 ± 177	2692 ± 309	3538 ± 225	3690 ± 303	4609 ± 120	32332 ± 2429	100%
II. Lomustine 50 mg/kg (n=12)	1430 ± 257 32% p=0.072	1649 ± 312 39% p=0.016	2372 ± 282 33% p=0.011	2426 ± 294 34% p=0.004	3000 ± 252 35% p=0.0004	22048 ± 2865 p<0.02	68% p<0.02

TI (%) – tumor growth inhibition, S – area under the tumor growth kinetic curve, TGI – tumor growth index (which is the ratio of S in the study group to S in the control group, expressed as a percentage).

Table 3

The effect of lomustine on the lifespan of FVB/N mice with an intracranially inoculated HER2+ breast cancer

Group	No of mice/live by day 27	MLS	95% CI	ILS
I. Control	12/0	21	14.2–27.8	-
II. Lomustine 50 mg/kg	10/7 (p=0.0007)	30	27.0–33.0 (p<0.001)	43 %

MLS – median of life span, ILS – increase of the life span, 95 % CI – 95 % confidence interval.

Results and Discussion

A single oral administration of lomustine at a dose of 50 mg/kg resulted in a significant inhibition of the growth of transplantable HER2-positive breast cancer (BC HER2+). On day 12 after inoculation (day 6 after lomustine injection), tumor growth inhibition reached 96 % ($p=0.0004$) and subsequently remained at a high level (Table 1), being 52 % on day 28 ($p<0.0001$). The area under the kinetic curve of tumor growth in mice treated with lomustine was 3 times less than that in the control group, and the tumor growth index (TGI) was 33 % (Table 1).

No pronounced effect of lomustine on the growth of intramuscularly transplanted Ehrlich tumor in BALB/c mice was observed (Table 2). After administration of lomustine at the dose of 50 mg/kg, the inhibition of Ehrlich tumor growth was statistically significant, but did not exceed 39 %. No pronounced effect of lomustine on Ehrlich tumor was found when the tumor growth index reached 68 % (Table 2).

The median survival of FVB/N mice with intracranially transplanted HER2+ breast cancer treated with lomustine was 43 % higher than that in the control group mice ($p<0.001$) (Table 3). On day

27 after inoculation, all 12 mice in the control group died. Of the 10 mice treated with lomustine, 7 were alive (70 %; $p=0.0007$).

Thus, lomustine showed a significant therapeutic effect on HER2-positive breast cancer in FVB/N Her-2 transgenic mice. However, the effect of lomustine on Ehrlich tumor in BALB/c mice was very moderate. The high activity of lomustine in FVB/N mice with transplanted HER-2 positive breast cancer is obviously can be explained by the biological characteristics of this tumor, thus suggesting that clinical trials of lomustine for HER-2 positive tumors are needed.

Conclusion

HER2-positive breast cancer in FVB/N Her-2 transgenic mice demonstrates significant sensitivity to lomustine in both extra- and intracranial tumor localization. The high therapeutic effect of lomustine on HER2-positive breast cancer in FVB/N Her-2 transgenic mice indicates the need for conducting clinical trials of lomustine in patients with HER2-positive tumors, including HER2-positive cancer with brain metastases.

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Conflict of interest

The authors declare that they have no conflict of interest.