PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2001;7(5):698-701
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORT •

Influence of L-methionine-deprived total parenteral nutrition with 5-fluorouracil on gastric cancer and host metabolism

Hong-Bing Xiao[1], Wei-Xin Cao[2], Hao-Ran Yin[2], Yan-Zhen Lin[2] and Shi-Hui Ye[1]

[1]Department of Surgery, Affiliated Railway Hospital, Tongji University, Shanghai 200072, China
[2]Department of Surgery, Affiliated Ruijin Hospital, Shanghai Second Medical University, Shanghai 200025, China
Supported by the National Natural Science Foundation of China, No.39370780.
Correspondence to: Dr. Hong-Bing Xiao, Department of Surgery, Affiliated Railway Hospital, Tongji University, Shanghai 200072, China. xhawbin@online.sh.cn
Telephone: +86-21-56533693, Fax: +86-21-56773983
Received 2001-05-06 **Accepted** 2001-06-20

Abstract

AIM **To investigate the influence of L-methionine-deprived total parenteral nutrition with 5-FU on gastric cancer and host metabolism.**

METHODS **N-methyl-N'-nitro-nitrosoguanidine (MNNG) induced gastric cancer rats were randomly divided into four groups: Met-containing TPN group (*n* = 11), Met-deprived TPN group (*n* = 12), Met-containing TPN+5-FU group (*n* = 11) and Met-deprived TPN+5-FU group (*n* = 12). Five rats in each group were sacrificed after 7 days of treatment and the samples were taken for examination. The remaining rats in each group were then fed separately with normal diet after the treatment until death, the life span was noted.**

RESULTS **The tumors were enlarged in Met-containing group and shrank in Met-deprived group markedly after the treatment. The DNA index (DI) of tumor cells and the body weight (BW) of rats had no significant change in the two groups, however, the ratio of tumor cells' S phase was increased. The ratio of G2M phase went up in Met-containing group, but down in Met-deprived group. In the other two groups that 5-FU was added, the BW of rats, and the diameter of tumors, the DI of tumor cells, the S and G2M phase ratio of tumor cells were all decreased, particularly in Met-deprived plus 5-FU group. Pathological examination revealed that the necrotic foci of the tumor tissue increased after Met-deprived TPN treatment, and the nucleoli of tumor cells enlarged. In -MetTPN+5-FU group, severe nuclear damage was also found by karyopyknosis and karyorrhexis, meanwhile there was slight degeneration in some liver and kidney cells. The serum free Met and Cysteine decreased markedly (*P*<0.001), while other amino acids, such as serum free serine and glutamine increased significantly (*P*<0.005). All the rats died of multiple organ failure caused by cancer metastasis. The average survival time was 18.6 days in Met-containing TPN group, 31 days in Met-deprived TPN group, 27.5 days in Met-containing TPN+5-FU group, and 43 days in Met-deprived TPN+5-FU group (*P*<0.05).**

CONCLUSION **Met-deprived TPN causes methionine starvation of tumor cells, and can enhance the anti-tumor effect of 5-FU and prolong the life span of gastric cancer-bearing rats.**

Subject headings stomach neoplasms/therapy; stomach neoplasms/pathology; parenteral nutrition; methionine/therapy use; fluorouracil/therapy use

Xiao HB, Cao WX, Yin HR, Lin YZ, Ye SH. Influence of L-methionine-deprived total parenteral nutrition with 5-fluorouracil on gastric cancer and host metabolism. *World J Gastroenterol*, 2001;7(5): 698-701

INTRODUCTION

Many tumor cells can not grow in the medium replaced L-methionine (Met) with its direct precursor L-homocyateine. However, normal cells can grow well in that medium. It means that the growth of tumor cell is Met-dependent[1-9]. In this study, we prepared a Met-free amino acid solution and used it as the sole nitrogen source of total parental nutrition (TPN), to investigate the influence of Met-deprived TPN on the gastric cancer and host metabolism.

MATERIALS AND METHODS

Animal grouping and treatment

Male Wistar rats, with N-methyl-N'-nitro-nitrosoguanidine (MNNG) induced gastric cancer (*n* = 46), were verified to have tumor diameter larger than 8 mm in laparotomy and confirmed pathologically. The 46 rats were randomly divided into four groups: Met-containing TPN group (*n* = 11), Met-deprived TPN group (*n* = 12), Met-containing TPN+5-FU group (*n* = 11) and Met-deprived TPN+5-FU group (*n* = 12). Five rats in each group were sacrificed after 7 d of treatment and the specimens were taken for examination and the other rats were then fed with normal diet separately after the treatment until death for noting the life span. After 24 h fasting, the rats were cannulated to the vena cava immediately after peritoneal cavity anesthesia with 25 $g \cdot L^{-1}$ barbital and placed in metabolic cage respectively and infused with different TPN solution after fixing the TPN tube at the back of rats with a plate and tension spring.

Composition and infusion of TPN solution

The rats were infused with 50 $g \cdot L^{-1}$ glucose normal saline 200 mL $\cdot kg^{-1}$ on the cannulation day. Different TPN solutions were infused continously 24 h a day on the next 7 d. During the experiment, the rats were housed individually in metabolic cages. The composition and usage of TPN solutions are shown in Table 1.

Specimen sampling and detection

Pre- and post- TPN, the rats' body mass (BM) and the tumor

diameter were measured, the tumor tissues were sampled for flow cytometry (FCM) tumor cell cycle analysis and DNA index calculation. Blood samples were taken for serum amino acid profile test. Tissues of the rats' gastric cancer, heart, lung, liver and kidney were sampled and fixed with 100 mL·L^{-1} formalin, enbedded with paraffin, sliced in 5 μm, and HE stained for pathohistologic examination.

Table 1 Composition and dosage of TPN solution (kg^{-1}·d^{-1})

Composition	+MetTPN	-MetTPN
250 g·L^{-1} Glucose / mL	100	100
200 g·L^{-1} Intralipid / mL	35	35
+Met amino acid solution / mL	100	0
-Met amino acid solution / mL	0	100
Non-protein energy / J	710	710
Total nitrogen / g	1.30	1.03
Total volume / mL	235	235

Usage and dose of 5-FU

5-FU was added to the TPN solution and infused for 6 d (from d 2 to d 7, 15 mg·kg^{-1}·d^{-1}).

Observation of survival time

The other rats in each group not sacrificed were moved to common cage after withdrawing TPN tube and fed with normal diet until death. The survival time was noted.

Statistical analysis

Student t test was used to examine the data. Survival time was examined with time sequence examination. The difference was considered significant when the *P* value was less than 0.05.

RESULTS

Alteration of the rats' BM, tumor size and DI

The BM and DI had no significant change in both +MetTPN and -MetTPN groups after treatment. The tumor size was markedly enlarged in +MetTPN group and shrank in -MetTPN group. All of the BM and the DI as well as the tumor size were decreased in both groups of +MetTPN+5-FU and -MetTPN+5-FU, and the change was more significant in the -MetTPN+5-FU group (Table 2).

Change of tumor cell cycles

The S phase percentage of tumor cells was increased in both +MetTPN and -MetTPN groups, and it is higher in the other groups. However, the change of G2M phase ratio was different. It was increased in +MetTPN group and decreased in -MetTPN group. The S and G2M phases were lowered in the other groups with 5-FU. The change was more significant in -MetTPN+5-FU group (Table 3).

Table 2 Body mass, tumor diameter and DNA index of tumor cells after TPN ($\bar{x}$±s)

TPN solution	mb / g		dt / mm		DNA index	
	Pre-TPN	Post-TPN	Pre-TPN	Post-TPN	Pre-TPN	Post-TPN
+MetTPN	242±20	243±20	11.2±1.0	14.7±0.7^{b}	1.13±0.24	1.21±0.26
-MetTPN	248±20	245±18	11.5±1.2	6.9±0.8^{ad}	1.15±0.21	1.12±0.23
+MetTPN+5-FU	245±13	233±12^{b}	11.1±1.1	9.3±0.8^{a}	1.15±0.03	1.08±0.02^{a}
-MetTPN+5-FU	245±14	225±13^{b}	11.4±0.9	5.5±0.5^{bc}	1.15±0.03	1.02±0.02^{bc}

^{d}P<0.05, ^{b}P<0.01, *vs* preTPN; ^{c}P<0.05, ^{d}P<0.01, *vs* +MetTPN.

Table 3 Change of tumor cell cycles after TPN ($\bar{x}$±s, %)

TPN solution	S		G2M		G0 / G1	
	Pre-TPN	Post-TPN	Pre-TPN	Post-TPN	Pre-TPN	Post-TPN
+MetTPN	6.2±1.2	10.3±1.4^{b}	10.5±1.1	16.6±1.4^{a}	83.4±1.9	73.1±1.8^{b}
-MetTPN	6.4±1.0	28.5±1.0^{ac}	11.2±1.1	8.3±1.5^{ad}	82.4±0.9	63.2±5.5^{a}
+MetTPN+5-FU	6.6±0.3	4.5±0.5^{a}	12.6±0.5	9.7±1.2^{a}	80.8±0.3	85.8±1.2^{b}
-MetTPN+5-FU	6.5±0.7	4.5±0.3^{a}	12.4±0.9	6.2±0.5^{bc}	80.1±0.5	89.3±0.7^{b}

^{a}P<0.05, ^{b}P<0.01, *vs* preTPN; ^{c}P<0.05, ^{d}P<0.01, *vs* +MetTPN.

Serum amino acid profile

The serum L-methionine and L-systein were markedly decreased in the -MetTPN rats. However, the other amino acids such as asprine and glutamine as well as serine were significantly increased after treatment (Table 4).

Pathohistological findings

The number of tumor necrotic foci were increased after -MetTPN and -MetTPN+5-FU treatment. Nuclei was enlarged in tumor cells and liver cells.

Survival time

All the gastric cancer bearing rats died of cancer metastasis and cachexia. The mean survival time was 18.6 d in +MetTPN group, 31 d in -Me tTPN, 27.5 d in +MetTPN+5-FU and 43 d in -MetTPN+5-FU (P<0.05).

Table 4 Serum FAA value ($\bar{x}$±$s_{\bar{x}}$, μmol·L^{-1})

	+MetTPN	-MetTPN
Asp	36.1±1.2	88.9±10.3^{a}
Glu	27.3±4.2	193.2±17.4^{a}
Ser	124.8±21.5	231.5±32.3^{a}
Gly	116.9±18.3	286.7±21.9^{a}
Gln	103.4±14.4	90.1±10.3
His	11.2±1.5	25.0±3.6
Thr	53.5±3.8	93.2±7.1^{a}
Ala	138.7±30.1	218.8±31.4^{a}
Arg	83.6±9.4	173.4±25.1^{a}
Pro	33.9±8.2	79.7±13.4
Tyr	20.8±5.1	44.8±6.3
Val	88.4±14.1	31.6±1.6
Met	76.1±1.3	10.9±3.1^{b}
Cys	87.3±3.2	43.2±5.4^{b}
Ile	5.4±1.1	10.1±1.2
Leu	34.2±1.3	55.2±4.3
Phe	22.1±2.2	43.1±2.9
Trp	42.5±3.6	50.7±4.4
Lys	212.4±43.1	387.8±58.3^{a}

^{a}P<0.05, ^{b}P<0.001, *vs* +MetTPN.

DISCUSSION

Patients with malignant tumors often show severe protein-amino acid metabolism disorder and uncorrectable negative nitrogen balance as well as low immune function caused by malnutrition[10-21]. TPN support is considered beneficial to improve the patients' nutritional status and immune function, and to lower the surgical complications, and to improve the quality of life[22-28]. But, TPN can also stimulate proliferation of the tumor cells[29,30]. So, there is much concern to study the special feature of tumor cells' metabolism and to find a regimen of TPN that is beneficial to the host, but pernicious to the tumor cells, particularly through the regulation of tumor cells' metabolism[31-52].

In this study, a special regimen of TPN deprived of Met was used in MNNG induced gastric cancer rats. The results showed that the TPN, containing Met or not, has regulative effects on the tumor cells' dynamics. The effects were different between Met-containing TPN and Met-deprived one. Met-containing TPN stimulated tumor cells' proliferation and promoted the tumor cells from G0/G1 phase into S and G2M phase, and made the ratio of S phase to G2M phase increased simultaneously. However, the Met-deprived TPN disturbed the metaboli sm of DNA, especially DNA methylation through Met starvation and inhibited the tumor proliferation by blunting S phase into G2M phase, resulting in increase of S phase ratio and decrease of G2M phase ratio. The inhibitory effect of tumor growth of the Met-deprived TPN was enhanced by simultaneous use of 5-FU, and it was manifested by a longer life span in the rats treated. Pathohistological examination found that the necrotic foci were increased in the tumor tissue and the nuclei of the tumor cells were enlarged. The pathohistologic findings were concordant with FCM analysis of cell cycles, meaning that the metabolism of DNA was blunted. One must be careful when using -MetTPN, particularly -MetTPN+5-FU, as some adverse effects may occur. In this practice, we noticed that the host liver and kidney cells had light degeneration. Hoffman *et al*[53] studied the growth of SV-40 fibroblast cells in the medium deprived of Met and found that the cell proliferation was blunted in S/G2 phase reversibly. Further studies[54] found that in the Met-free environment, the intracellular free Met of tumor was extremely decreased and it lowered greatly the S-Adeosylmethionine (S-AdoMet) which had decreased because of the tumor cell's over active transmethylation, and resulted in a low ratio of S-AdoMet to S-AdoHcy. This directly inhibited the activity of transmethylase and suppressed the transmethylation reaction, including the DNA methylation. When the tumor cells were returned to the Met-containing environme nt, DNA methylation recovered and the cell cycle circulated. This reversible block of tumor cell cycle at S/G2 phase enhanced the anti-cancer effect of 5-FU and hinted the combined and sequenced use of other cycle specific chemotherapy agents with Met-deprived TPN.

By autopsy, we found that the liver and peritoneum metastasis of gastric cancer were much less in the group using Met-deprived TPN and the group using Met-deprived TPN plus 5-FU. It suggests that not only the primary tumor proliferation was inhibited, but also the invasive ability for metastasis was suppressed. Breillout *et al*[55] reported that Met-deprived TPN suppressed the metastasis potential of Lewis lung cancer and rhabdomyosarcoma in experimental animals. They considered that it was Met-starvation which disturbed the methylation of DNA and membrane lipids of the tumor cells, inhibiting their metastastic ability. Some authors even suggested that the inhibitory effect of -MetTPN against metastasis is more powerful than in proliferation of primary tumors. However, this still needs further studies.

REFERENCES

1 Sakagami H, Satoh K, Fukuchi K, Kadofuku T, Gomi K, Nakamura K, Kuribayashi N, Sunaga S, Hirota N, Iida M, Makino Y, Kojima T, Shimura H, Takeda M. Effect of methionine depletion on growth and apoptosis in various tumor cell lines. *Anticancer Res*, 1997;17:2407-2410

2 Hoshiya Y, Guo H, Kubota T, Inada T, Asanuma F, Yamada Y, Koh J, Kitajima M, Hoffman RM. Human tumors are methionine dependent *in vivo*. *Anticancer Res*, 1995;15:717-718

3 Poirson-Bichat F, Gonfalone G, Bras-Goncalves RA, Dutrillaux B, Poupon MF. Growth of methionine-dependent human prostate cancer (PC-3) is inhibited by ethionine combined with methionine starvation. *Br J Cancer*, 1997;75:1605-1612

4 Khomutov RM, Zhukov IN, Khomutov AR, Khurs EN, Kramer DL, Miller JT, Porter CW. Phosphinic analog of methionine inhibits growth of leucosis cell L1210 and transforms to phosphinic analog of S-adenosylmethionine. *Bioorg Khim*, 2000;26:718-720

5 Usami M, Ohyanagi H, Ishimoto S, Nishimatsu S, Ueda T, Saitoh Y. Effect of methionine-deprived nutrition on cell growth and cell kinetics in cell cultures and experimental tumors. *J Parenter Enteral Nutr*, 1991;15:540-545

6 Poirson-Bichat F, Lopez R, Bras Goncalves RA, Miccoli L, Bourgeois Y, Demerseman P, Poisson M, Dutrillaux B, Poupon MF. Methionine deprivation and methionine analogs inhibit cell proliferation and growth of human xenografted gliomas. *Life Sci*, 1997;60:919-931

7 Millis RM, Diya CA, Reynolds ME. Growth inhibition of subcutaneously tran splanted hepatomas by alterations of the dietary arginine-methionine balance. *Nutr Cancer*, 1996;25:317-327

8 Kokkinakis DM, von Wronski MA, Vuong TH, Brent TP, Schold SC Jr. Regulation of O6-methylguanine-DNA methyltransferase by methionine in human tumour cells. *Br J Cancer*, 1997;75:779-788

9 Tang B, Li YN, Kruger WD. Defects in methylthioadenosine phosphorylase are associated with but not responsible for methionine-dependent tumor cell growth. *Cancer Res*, 2000;60:5543-5547

10 Mulligan K, Bloch AS. Energy expenditure and protein metaboli sm in human immunodeficiency virus infection and cancer cachexia. *Semin Oncol*, 1998;25(2 Suppl 6):82-91

11 Samuels SE, Knowles AL, Tilignac T, Debiton E, Madelmont JC, Attaix D. Protein metabolism in the small intestine during cancer cachexia and chemotherapy in mice. *Cancer Res*, 2000;60:4968-4974

12 Soeters PB, de Blaauw I, van Acker BA, von Meyenfeldt MF, Deutz NE. *In vivo* inter-organ protein metabolism of the splanchnic region and muscle during trauma, cancer and enteral nutrition. *Baillieres Clin Endocrinol Metab*, 1997;11:659-677

13 Daley SE, Pearson AD, Craft AW, Kernahan J, Wyllie RA, Price L, Brock C, Hetherington C, Halliday D, Bartlett K. Whole body protein metabolism in children with cancer. *Arch Dis Child*, 1996;75:273-281

14 Preston T, Fearon KC, McMillan DC, Winstanley FP, Slater C, Shenkin A, Carter DC. Effect of ibuprofen on the acute-phase response and protein metabo lism in patients with cancer and weight loss. *Br J Surg*, 1995;82:229-234

15 Karayiannakis AJ, Syrigos KN, Polychronidis A, Pitiakoudis M, Bounovas A, Simopoulos K. Serum levels of tumor necrosis factor-alpha and nutritional status in pancreatic cancer patients. *Anticancer Res*, 2001;21:1355-1358

16 Jagoe RT, Goodship TH, Gibson GJ. The influence of nutritional status on complications after operations for lung cancer. *Ann Thorac Surg*, 2001;71:936-943

17 Jagoe RT, Goodship TH, Gibson GJ. Nutritional status of patients und ergoing lung cancer operations. *Ann Thorac Surg*, 2001;71:929-935

18 Su LJ, Arab L. Nutritional status of folate and colon cancer risk: evidence from NHANES I epidemiologic follow-up study. *Ann Epidemiol*, 2001;11:65-72

19 Kim KK, Yu ES, Chen EH, Cross N, Kim J, Brintnall RA. Nutritional status of Korean Americans: implications for cancer risk. *Oncol Nurs Forum*, 2000;27:1573-1583

20 Hatada T, Miki C. Nutritional status and postoperative cytokine response in colorectal cancer patients. *Cytokine*, 2000;12:1331-1336

21 van Bokhorst-de van der Schuer, van Leeuwen PA, Kuik DJ, Klop WM, Sauerwein HP, Snow GB, Quak JJ. The impact of nutritional status on the prognoses of patients with advanced head and neck cancer. *Cancer*, 1999;86:519-527

22 Federico A, Iodice P, Federico P, Del Rio A, Mellone MC, Catalano G. Effects of selenium and zinc supplementation on nutritional status in patients with cancer of digestive tract. *Eur J Clin Nutr*, 2001;55:293-297

23 van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, Kuik DJ, Langendoen SI, Snow GB, Green CJ, van Leeuwen PA. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severel y malnourished head and neck cancer patients. *Am J Clin Nutr*, 2001;73:323-332

24 Bozzetti F, Cozzaglio L, Gavazzi C, Bidoli P, Bonfanti G, Montalto F, Soto Parra H, Valente M, Zucali R. Nutritional support in patients with cancer of the esophagus: impact on nutritional status, patient compliance to therapy, and survival. *Tumori*, 1998;84:681-686

25 Shirai R, Kadota J, Iida K, Kawakami K, Abe K, Yoshinaga M, Iwashita T, Matsubara Y, Oka M, Kohno S. Immunological competence and nutritional stat us in patients with lung cancer. *Lung*, 1998;176:363-370

26 den Broeder E, Lippens RJ, van't Hof MA, Tolboom JJ, van Staveren WA, Hofman Z, Sengers RC. Effects of naso-gastric tube feeding on the nutriti onal status of children with cancer. *Eur J Clin Nutr*, 1998; 52:494-500

27 Doerr TD, Marks SC, Shamsa FH, Mathog RH, Prasad AS. Effects of zinc and nutritional status on clinical outcomes in head and neck cancer. *Nutrition*, 1998;14:489-495

28 Lai SL, Perng RP. Impact of nutritional status on the survival of lung cancer patients. *Zhonghua Yixue Zazhi (Taipei)*, 1998;61:134-140

29 Chance WT, Zhang X, Zuo L, Balasubramaniam A. Reduction of gut hypoplasia and cachexia in tumor-bearing rats maintained on total parenteral nutrition and treated with peptide YY and clenbuterol. *Nutrition*, 1998;14:502-507

30 Bozzetti F, Gavazzi C, Cozzaglio L, Costa A, Spinelli P, Viola G. Total parenteral nutrition and tumor growth in malnourished patients with gastric cancer. *Tumori*, 1999;85:163-166

31 Cao WX, Cheng QM, Fei XF, Li SF, Yin HR, Lin YZ. A study of preope rative methionine-depleting parenteral nutrition plus chemotherapy in gastric cancer patients. *World J Gastroenterol*, 2000;6:255-258

32 Zhu SS, Xiao SD, Chen ZP, Shi Y, Fang JY, Li RR, Mason JB. DNA methylation and folate metabolism in gastric cancer. *World J Gastroenterol*, 2000;6(Suppl 3):18

33 Forchielli ML, Paolucci G, Lo CW. Total parenteral nutrition and home parenteral nutrition: an effective combination to sustain malnourished children with cancer. *Nutr Rev*, 1999;57:15-20

34 Chance WT, Ogle CK, Thomas I, Zhou L, Zhang X, Basanta M, Fischer JE. Immunostimulation following fish oil-based parenteral nutrition in tumor-bearing rats. *Nutr Cancer*, 1996;26:303-312

35 Goseki N, Nagahama T, Maruyama M, Endo M. Enhanced anticancer effe ct of vincristine with methionine infusion after methionine-depleting total parenteral nutrition in tumor-bearing rats. *Jpn J Cancer Res*, 1996;87:194-199

36 Nagahama T, Goseki N, Endo M. Doxorubicin and vincristine with methionine depletion contributed to survival in the Yoshida sarcoma bearing rats. *Anticancer Res*, 1998;18:25-31

37 Goseki N, Yamazaki S, Endo M, Onodera T, Kosaki G, Hibino Y, Kuwahata T. Antitumor effect of methionine-depleting total parenteral nutrition with doxorubicin administration on Yoshida sarcoma-bearing rats. *Cancer*, 1992;69:1865-1872

38 Goseki N, Endo M, Onodera T, Kosaki G. Anti-tumor effect of L-methi onine-deprived total parenteral nutrition with 5-fluorouracil administration on Yoshida sarcoma-bearing rats. *Ann Surg*, 1991; 214:83-88

39 Goseki N, Maruyama M, Nagai K, Kando F, Endo M, Shimoju K, Wada Y. Clinical evaluation of anticancer effect of methionine -depleting total parenteral nutrition with 5-fluorouracil and / or mitomycin C. *Gan To Kagaku Ryoho*, 1995;22:1028-1035

40 Goseki N, Endo M. Thiol depletion and chemosensitization on nimustine hydrochloride by methionine-depleting total parenteral nutrition. *Tohoku J Exp Med*, 1990;161:227-239

41 Hibino Y, Kawarabayashi Y, Kohri H, Ueda N, Tsukagoshi S. The mec hanism of potentiation of the antitumor effect of 5-fluorouracil by methionine -free intravenous amino acid solution (AO-90) in rats. *Gan To Kagaku Ryoho*, 1994;21:2021-2028

42 Oka T, Ohwada K, Nagao M, Kitazato K. Effect of arginine-enriched total parenteral nutrition on the host-tumor interaction in cancer-bearing rats. *J Parenter Enteral Nutr*, 1993;17:375-383

43 Stallion A, Foley-Nelson T, Chance WT, Zhang FS, Fischer JE. Parenteral *vs* enteral nutrition in tumor-bearing rats. *J Parenter Enteral Nutr*, 1994;18:148-153

44 Chance WT, Cao LQ, Fischer JE. Response of tumor and host to hypera limentation and antiglutamine treatments. *J Parenter Enteral Nutr*, 1990;14:122-128

45 Yoshida S, Ishibashi N, Noake T, Shirouzu Y, Oka T, Shirouzu K. Glutamine and arginine metabolism in tumor-bearing rats receiving total parenteral nutrition. *Metabolism*, 1997;46:370-373

46 Yoshida S, Yamasaki K, Kaibara A, Takagi K, Noake T, Ishibashi N, Kakegawa T. Effect of methionine-deprived total parenteral nutrition on tumor protein turnover in rats. *Cancer*, 1995;76:1275-1282

47 Goseki N, Yamazaki S, Shimojyu K, Kando F, Maruyama M, Endo M, Koike M, Takahashi H. Synergistic effect of methionine-depleting total parenteral nutrition with 5-fluorouracil on human gastric cancer: a randomized, prospective clinical trial. *Jpn J Cancer Res*, 1995;86:484-489

48 Komatsu H, Nishihira T, Chin M, Doi H, Shineha R, Mori S, Satomi S. Effect of valine-depleted total parenteral nutrition on fatty liver development in tumor-bearing rats. *Nutrition*, 1998;14:276-281

49 Kaibara A, Yoshida S, Yamasaki K, Ishibashi N, Kakegawa T. Effect of glutamine and chemotherapy on protein metabolism in tumor-bearing rats. *J Surg Res*, 1994;57:143-149

50 Oka T, Ohwada K, Nagao M, Kitazato K, Kishino Y. Arginine-enriched solution induces a marked increase in muscle glutamine concentration and enhances muscle protein synthesis in tumor-bearing rats. *J Parenter Enteral Nutr*, 1994;18:491-496

51 Sasamura T, Matsuda A, Kokuba Y. Nutritional effects of a D-methionine-containing solution on AH109A hepatoma-bearing rats. *Biosci Biotechnol Biochem*, 1998;62:2418-2420

52 Nishihira T, Takagi T, Mori S. Leucine and manifestation of antitumor activity by valine-depleted amino acid imbalance. *Nutrition*, 1993;9:146-152

53 Hoffman RM, Jacobsen SJ, Erbe RW. Reversion to methionine independence by malignant rat and SV40-transformed human fibroblasts. *Biochem Biophys Res Commun*, 1978;82:228-234

54 Hoffman RM. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis: a review and synthesis. *Biochim Biophys Acta*, 1984;738:49-87

55 Breillout F, Antoine E, Poupon MF. Methionine dependency of malignant tumors: a possible approach for therapy. *J Natl Cancer Inst*, 1990;82:1628-1632

Edited by Ma JY