

Prognostic value of glutathione-s-transferase during medicamentous treatment of advanced lung cancer

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ABSTRACT

Has been studied glutathione-s-transferase as prognostic factor at medicamentous treatment of advanced lung cancer. Has been stated the level of glutathione-s-transferase in healthy individuals' blood that ranges widely from 41 to 1,13 nmol/min/ml. Has been revealed correlation between glutathione-s-transferase activity and efficacy of carried out treatment. Treatment is less effective at high concentration of the above-mentioned marker in blood; discrimination level of glutathione-s-transferase in patients with lung cancer is 1,5 nmol/min/ml; On the basis of received data, detection of DST in blood serum of patients with advanced lung cancer is recommended for prognostic evaluation of cancer's sensitivity to medicamentous treatment.

KEYWORDS: *lung cancer, chemotherapy, prognostic factor*

In molecular biology the last decade discoveries drastically influenced one of the major problems of oncology - understanding of mechanisms of medicamentous resistance of malignant tumors.

Has been revealed that presence or absence of certain molecular markers in cancer cells indicates following - according to the TNM classification cancers of the same stage differ by disease course aggression and sensitivity toward antitumor medicamentous treatment. Naturally, it makes difficult to select optimal treatment for concrete patient.

Detection of cancers individual peculiarities makes available to elaborate treatment measures for oncological patient according to its genetic indices.

Nowadays, searching of such markers and detection of their prognostic and predicting (predictor of sensitivity to treatment with concrete drugs) role is very topical.

There are numerous predicting factors (oncogenes, growth factor, enzymes etc.) and prognostic criteria facilitating selection of adequate treatment (Isquierdo et al, 1995; Possinger, 1998; Cappuzzo et al, 2004; Pao et al, 2004).

Mechanism of development of malignant tumor's resistance against cytostatics is intracellular detoxication of preparations due to triggering of enzymes' cascade. Among them glutathione-s-transferase play the decisive role (GST) (Larionova et al., 2000; Kurpeshev et al., 2002; Bendel et al, 2005).

The aim of present work is the revelation of prognostic value of glutathione-s-transferase at advanced lung cancer.

MATERIAL AND METHODS

A total of 28 patients suffering from advanced lung cancer were investigated. Among them 20 patients, according to the histomorphology, had non small-cell lung cancer (NSCLC), 4 - small-cell lung cancer (SCLC) and 4 case was not verified. Of 28 patients, 8 were female and 20 - male, age range was from 42 to 72 years. III stage cancer was detected in 12 cases, IV stage - in 16 cases.

In order to establish diagnosis and detect process spread, patients were subjected to complex examination: Chest X-ray, in most cases - CT and all required laboratory testing.

Main schemes of treatment were:

1. Taxol - 175 mg/m² first day
Cisplatin - 80 mg/ml first day
2. Navelbin - 25-30 mg/m² first and eighth day
Cisplatin - 80 mg/ml first day
3. Etoposid - 120 mg/m² first, third and fifth day
Cisplatin - 80 mg/ml first day
Cyclophosphane - 600 mg/m² third and fifth day
4. Cyclophosphane - 1000 mg/m² first day
Adriablastine - 30 mg/m² first day
Vinkristin - 1 mg/m² first day

Cours was repeated every 3-4 weeks. Treatment efficacy was evaluated according to the objective and subjective criteria (Sirkin, 2000).

Has been used Caiman Chemical Company GST set of reactives, determining total GST-activity.

GST- activity was defined according to the following formula:

$$\text{GSTact} = \frac{\Delta A_{340}/\text{min}}{0,00503 \text{ mcM}^{-1}} \times \frac{0,2 \text{ ml}}{0,02 \text{ ml}} \times \text{sample dilution} = \text{nmol/min/ml}$$

where 0,00503 mcM⁻¹ is CDNB coefficient of extinction. One unit of enzyme conjugates with 1,0 nmol CDNB reduced glutathione per minute at 25°C.

Received data have been analyzed using the variation statistic methods. Results' significance has been evaluated by Student's t test.

RESULTS AND DISCUSSION

First of all we have studied levels of GST activity in healthy individuals. Has been revealed significant variability - from 0,41 to 1,13 nmol/min/ml. The mean value consisted 0,78±0,16 nmol/min/ml.

Glutathione-s-transferase activity in lysed erythrocytes and plasma of healthy individuals and patients with lung cancer before treatment are presented on Fig.1.

As it has shown, GST activity in plasma and lysed erythrocytes practically coincides. GST activity in erythrocytes is slightly elevated, as in case of healthy individuals, it is the result of intense staining of lysed erythrocytes.

Increased level of GST activity in the blood of patients with advanced lung cancer before treatment, compared to healthy individuals, could be related to the fact that 4 patients involved in investigations had the high level of the above-mentioned index from the beginning.

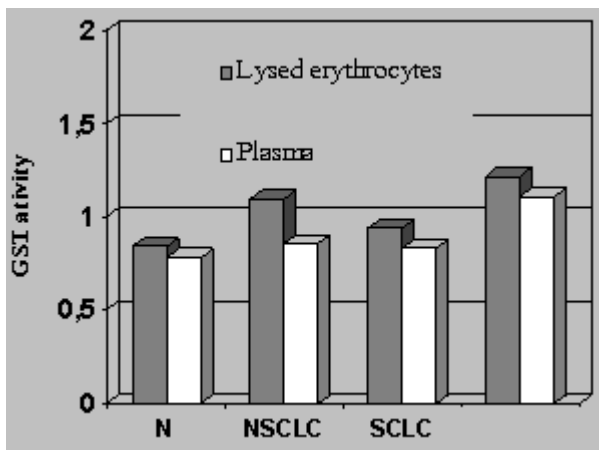


Fig.1 GST – activity in the blood of healthy individuals (N) and patients with advanced lung cancer before treatment: NSCLC – non small-cell lung cancer, SCLC - small-cell lung cancer.

Indices of patients' treatment efficacy after 5 course of chemotherapy are presented on Fig.2.

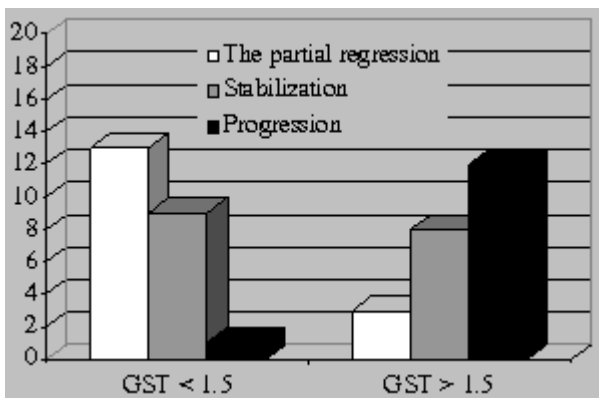


Fig.2 Ratio of partial effect, stabilisation and progression according to the GST levels (n=23).

As it has shown, there is no complete regression of cancer locus. The partial regression at low level of GST activity (<1,5 nmol/min/ml) was detected in 56,5% of cases; stabilization was revealed in 39,1% of cases and progression - in 4,4% of cases. At high level of GST (>1,5 nmol/min/ml) reduction of partial regression cases (13,0%) and elevation of progress persantage (52,2%) have been detected. In fact, treatment effect was positive when GST-activity was low. Meanwhile, according to the obtained results, detection of GST activity after first course of treatment makes available to evaluate in advance and predict efficacy of further course of treatment.

Treatment results by the end of examination are presented on the Fig.3.

As it has shown, in the died group were involved patients who had the high GST activity (2,08±0,62), range — 1,8-3,2 nmol/min/ml. Survival patients were subdivided into two major groups: with disease progression and without disease progression.

In the group with disease progression patients mean index of GST activity was

1,81±0,58, range — 1,5-2,1 nmol/min/ml, and in the group without disease progression patients mean index of GST activity was low (0,97±0,19), range — 0,66-1,5 nmol/min/ml.

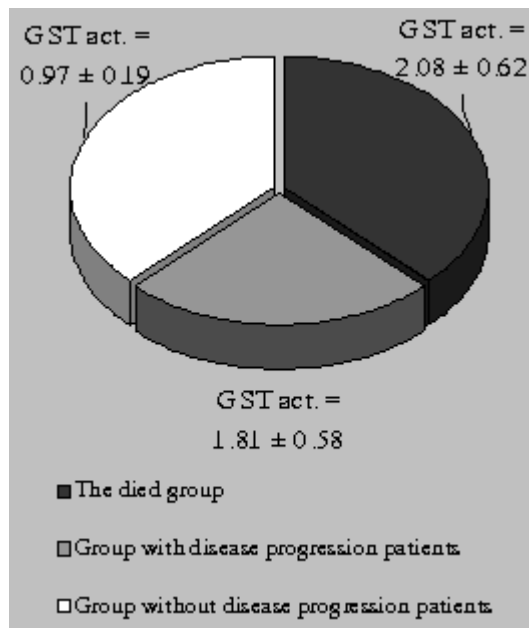


Fig.3 Patients' state and GST activity at the end of observation.

Because patients with stable state the highest level of GST activity was 1,5 nmol/min/ml, the mentioned level was assumed as discrimination level for GST activity.

The sum of cases with clinical effect of treatment and corresponding mean value of GST activity index, and sum of cases without clinical effect of treatment and corresponding mean value of GST activity index have shown on the Tab.1.

Treatment effect	GST-activity, nmol/min/ml
Positive n=43	1.3 ± 0.5
Negative n=38	2.1 ± 0.8*

p<0.001

Tab.1 Value of GST activity index.

Thus, the obtained results have shown significant correlation between GST activity level in plasma and effect of medicamentous treatment at advanced lung cancer.

Cancer progression is associated with increase in blood plasma GST activity. Our results have shown that detection of GST activity in plasma technically subordinates standartization, quite simple to perform and is able to replenish and enrich prognostic methods of medicamentous treatment of malignant tumors and among them patients suffering from advanced lung cancer.

On the basis of received data, detection of DST in blood serum of patients with advanced lung cancer is recommended for prognostic evaluation of cancer's sensitivity to medicamentous treatment.

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Прогностическое значение глутатион-S-трансферазы при лекарственном лечении распространенного рака легкого

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РЕЗЮМЕ

Изучено значение глутатион-S-трансферазы, как прогностического маркера при лечении распространенного рака легкого. Установлен уровень GST в крови здоровых лиц, который варьирует в довольно широких пределах, от 0,41 до 1,13 нмоль/мин/мл; выявлена корреляция между уровнем GST-активности и эффективностью проведенного лечения: при высокой концентрации этого маркера в крови лечение менее эффективно. Установлен дискриминационный уровень GST в крови больных раком легкого, который составил 1,5 нмоль/мин/мл. Полученные данные дают основание рекомендовать определение GST-активности в плазме крови больных раком легкого с целью прогностической оценки чувствительности опухоли к лекарственному лечению.

Ключевые слова: рак лёгкого, химиотерапия, прогностические оценки

□ **International committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals.** Ann Intern Med 1997;126:36–47.

Editors may find the following recommendations useful as they seek to establish policies on these issues.

1. *Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication in the journal, in return for which the journal will cooperate with them in preparing accurate stories (see below).*

2. *Very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. In such exceptional circumstances, however, appropriate authorities responsible for public health should make the decision and should be responsible for the advance dissemination of information to physicians and the media. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors accept the need for immediate release, they should waive their policies limiting prepublication publicity.*

3. *Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Redundant or Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters, but they should be discouraged from offering more detail about their study than was presented in their talk.*

4. *When an article is soon to be published, editors may wish to help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the journal, or referring reporters to the appropriate experts. This assistance should be contingent on the media's cooperation in timing their release of stories to coincide with the publication of the article.*

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