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Implication of the bioelectronic principle in cancer therapy : treatment of cancer patients by methylglyoxal-based formulation

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Abstract : Based on our previous *in vitro* studies with human cells and *in vivo* studies with animals we had developed an anticancer formulation with methylglyoxal as the lead ingredient. This formulation has a tumoricidal effect by inhibiting specifically in cancerous cells, the electron flow and the transfer of reducing equivalent necessary for the production of adenosine-5'-triphosphate (ATP), the cellular energy currency. By keeping this remarkable property in mind, we had treated 24 patients suffering from different types of malignancy (mostly in very advanced stage of the disease) with this methylglyoxal-based formulation. The results indicate a dramatic positive effect on the patients Out of the 24 patients, 11 are in excellent physical condition, the condition of 5 patients can be considered stable. The rest had either opted out from the treatment or died during the course of study These results strongly suggest that this formulation is by far more superior than other present forms of treatment against cancer. It is imperative that this formulation be widely used in treating cancer patients, as well as to attempt the improvement of its efficacy.

Keywords : Cancer therapy, bioelectronic principle, methylglyoxal

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1. Introduction

As early as 1958, the anticancer property of ketoaldehydes (such as methylglyoxal) and their derivatives were first studied and effective response was obtained [1]. Szent-Györgyi and his collaborators in their pioneering work on the biological role of methylglyoxal had put forward strong evidences for the anticancer and growth inhibitory effect of methylglyoxal [2]. It had been suggested that the anticancer property of methylglyoxal is due to its growth inhibitory effect. Szent-Györgyi had also suggested that proteins could act as electronic conductors and also pointed out the relationship of the loss of this properties with cancer. Moreover, the difference between normal differentiated cells and cancerous cells could be due to the deficiency of certain chemicals notably methylglyoxal and ascorbic acid in cancerous cells [2].

Együd and Szent-Györgyi showed that methylglyoxal could completely inhibit the tumor development in mice. When methylglyoxal was injected into mice along with sarcoma 180 cells, no tumor developed and the mice remained completely healthy [3]. At the same time, Apple and Greenberg with their remarkable experiments showed that methylglyoxal significantly inhibited tumor growth and in some cases produced indefinite survivors among mice bearing leukemia, lymphosarcoma, adenocarcinoma, sarcoma 180 and other varieties of tumors at daily dose level of approximately 80 mg/kg of body weight. Single dose of about 225 mg/kg of body weight significantly inhibited advanced leukemia and produced indefinite survivors among mice bearing either lymphosarcoma or carcinoma [4,5]. Similar therapeutic activity of methylglyoxal towards cancer bearing animals had also been obtained by other

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investigators [6]. Moreover, carcinostatic activity of methylglyoxal had been demonstrated convincingly in *in vitro* experiments with wide variety of cancerous cells obtained from animals ([6], for a review Ref. [7]). However, it is to be noted that almost all the above-mentioned studies had been done with animal systems and practically no studies had been conducted with human materials.

But subsequent experiments from our laboratory had clearly demonstrated that methylglyoxal is tumoricidal [8]. It had been observed with *in vitro* study that methylglyoxal inhibits both mitochondrial respiration and glycolysis of both human and animal malignant tissues and cells [9,10]. Methylglyoxal inhibits specifically in malignant cells the electron flow through complex I of the mitochondrial respiratory chain and also the transfer of reducing equivalent necessary for the generation of ATP, the energy currency of living cells [8–12]. As a consequence of inhibition of mitochondrial respiration and glycolysis, the ATP level of these cells are critically reduced, rendering them non-viable [9,10]. It has also been observed that ascorbic acid significantly augmented the tumorical effect of methylglyoxal [8]. On the other hand, under identical experimental conditions, methylglyoxal had no effect on the respiration and glycolysis of normal (nonmalignant) tissues and cells [8,10].

By using both *in vitro* and *in vivo* experiments, the results obtained from different studies as described above, convincingly demonstrated that methylglyoxal is a potent anticancer agent. Methylglyoxal acts selectively against malignant cells, sparing the normal cells. Its effect can be significantly augmented with natural compound(s), ascorbic acid and other vitamins. Moreover, methylglyoxal is well tolerated by both normal and tumor bearing animals, which is in sharp contrast to the properties of other anticancer drugs now widely used in the treatment of cancer patients. Despite all these results, it is very surprising and unfortunate, that neither the potentiality of methylglyoxal as an anticancer drug had been seriously investigated, nor its human trial had been initiated.

However, we have developed an anticancer formulation with methylglyoxal as the lead ingredient and have tested its potential to treat cancer patients and have obtained very encouraging results. These patients were suffering from different types of cancer and mostly were in very advanced stage of the disease. Almost all the patients who had received our treatment had shown marked improvement in their conditions. Biochemical and other relevant tests were done, prior to, during and after the treatment. The results of these tests had also shown that the different parameters indicating the patients conditions have come to almost normal level after the treatment.

The present paper describes the composition of the formulation, its dose regimen and treatment schedule, conditions of the patients and the results of the treatment.

2. Materials and methods

2.1. Patients :

Total 24 patients, both male and female in the age group of 32–78 yrs received the treatment with the present formulation (see below). They were inducted for the trial from January to June 2000. The patients had different types of malignancy confirmed by biopsy and in most of the cases metastatic carcinoma. A few of the patients had received no prior treatment; others had received treatment of surgery and/or radiotherapy and/or conventional chemotherapy; but almost all had no improvements. Their conditions worsened and there were many relapsed cases.

All the patients gave informed consent to participate in the treatment by the present formulation, the protocol of which had been approved by the Institutional Ethical Committee of Indian Association for the Cultivation of Science. The Drug Controller General (India) had also indicated no objection in the study.

2.2. Composition and treatment schedule of the formulation

A stock solution of 0.4–0.45 M methylglyoxal is essentially the main component of the present formulation. Each adult patient received orally at a time 10–12 ml of 0.4–0.45 M methylglyoxal diluted in 50–70 ml of water, followed by tablet of chewable vitamin C containing 400 mg of ascorbic acid. The patient received this treatment 4 times/day at regular interval. This is equivalent to the ingestion of 20–25 mg methylglyoxal/kg of body wt./day. Each patient also received orally a mixture of the following vitamins twice a day : B_1 5mg, B_2 5mg, B_6 2.5mg, B_{12} 5mcg and B_5 7.5mg. This treatment was continued for six consecutive days. In some cases, there was no treatment for 1 or 2 days before another six days of treatment in a similar fashion began. In other cases the treatment continued without any interruption.

The above-mentioned schedule of treatment continued for 8–10 weeks. Thereafter the amount of methylglyoxal ingested was reduced to 14–16 mg/kg/day which was divided in 3 doses in the dilution as mentioned above. After each ingestion of methylglyoxal, the patient received one tablet of chewable vitamin C corresponding to 400 mg of ascorbic acid. The supplementation of other vitamins continued as before. This schedule continued for another 15 weeks. Depending on the condition of the patients, the treatment was either discontinued or continued with further low dose of the present formulation.

2.3. Assessment of response to treatment :

Appropriate physical and biochemical examination as well as general well being of the patients did assessment of

response to the treatment. Biochemical, pathological and other physical tests of the patients were done in approved clinical laboratories.

2.4. Materials :

Methylglyoxal (pyruvaldehyde) was obtained from Sigma Chemical Co. St. Louis, MO, USA. Ascorbic acid (vitamin C) and other vitamins were products of different pharmaceutical companies and obtained from local medicine shops.

3. Results

The results of the treatment of 24 patients with the formulation and schedule of treatment as described in the materials and methods are summarised in Table 1. The study was made with patients, suffering from various types of malignancies affecting different organs of the body. The conditions of the patients described herein are at the time of submitting the present manuscript for publication. It appears from the result that 11 of the 24 patients treated are in 'excellent' physical condition; the conditions of 5 patients can be considered 'good'. Three patients died during course of the treatment and 5 patients opted out from the study. We considered the conditions of the patients as excellent, where the patients are leading almost normal life and the disease is apparently in remission. Good condition here indicates that although the patients have some ailments, these are at present not life-threatening and their conditions are more or less stable. Moreover it appears that these ailments are mainly due to the damage already caused by malignancy and/or by the previous treatment of chemo- or radiotherapy.

In addition to the summary of the results as presented in Table 1, some comments on the condition of some specific cases seems worthwhile.

Patient no. 17 : Very good response was observed within 7 days of the treatment. The patient was active and mobile and in generally good physical condition. However, the condition deteriorated suddenly two weeks before death; died September 2000.

Patient no. 18 : Good preliminary response, there was alleviation of breathing trouble; but the patient died probably due to the progression of the disease.

Patient no. 21 : There was significant improvement after only 1 course of the treatment, but the patient opted out after five courses and died in August 2000.

Table 1. Characteristics of the patients and outcome of the treatment (for further details see text).

Patient no	Age/Sex	Diagnosis	Time of detection	Previous treatment received	Commencement of the present treatment	Present condition
	32/M	Adenocarcinoma of colon, metastasis to liver (both lobes)	October 1999	Surgical resection of tumor, palliative treatment suggested	January 2000	Excellent
	73/F	Acute myeloid leukemia	Do	Palliative treatment suggested due to very poor physical condition	Do	Do
	46/M	Non-Hodgkin's lymphoma, metastasis to lung and possibly to liver (relapsed case)	December 1998	Chemotherapy twice without response	February 2000	Do
	72/F	Mucin-secreting adenocarcinoma of colon, metastasis to liver, pericolic lymph nodes and gall bladder	December 1999	A portion of the colon and gall bladder excised. Palliative treatment suggested	Do	Do
	40/F	Adenocarcinoma of ovary (relapsed after one year) with metastasis to omentum and peritoneal seeding	December 1998	Ovaries removed followed by chemotherapy. After relapse chemotherapy was non-responsive	March 2000	Do
	40/F	Serous cell adenocarcinoma of ovary (left), recurrence in right ovary during chemotherapy	January 2000	Surgical removal of left ovary, chemotherapy non-responsive, surgical removal of right ovary	Do	Do
	62/F	Infiltrating duct carcinoma of breast with metastasis in axillary lymph node and bone (stage IIIB)	Do	Mastactomy done followed by radiation	April 2000	Do
	56/F	Infiltrating duct carcinoma of breast with metastasis in lymph node and lung (stage IIIB-IV)	Do	Mastactomy done. Patient refused chemotherapy	Do	Do

Table 1. *(Cont'd)*

Patient no	Age/Sex	Diagnosis	Time of detection	Previous treatment received	Commencement of the present treatment	Present condition
9	36/M	Papillary transitional cell carcinoma, 4th time recurrence	Do	Surgery followed by chemotherapy twice After 4th recurrence patient refused chemotherapy	April 2000	Do
10	54/F	Multiple myeloma (relapsed) osteoporosis	December 1998	2nd time chemotherapy did not respond	May 2000	Good
11	61/M	Colorectal carcinoma	December 1999	Surgical removal, external colestomy bag Patient refused chemotherapy due to poor physical condition	Do	Excellent
12	35/M	Ampullary carcinoma of liver, metastasis to pancreas with billiary obstruction	May 2000	Endoscopic retrograde cholecysto pancreatography (ERCP)–steinting done, suggested palliative treatment	Do	Good
13	72/M	Hepatocellular carcinoma	March 2000	Palliative treatment suggested	May 2000	Excellent
14	70/F	Adenocarcinoma of colon, metastasis to liver and probably also in bone marrow	May 2000	Do	June 2000	Good
15	78/M	Squamous cell carcinoma of tongue (recurrence in Nov 1999)	December 1998	Chemotherapy given on first detection, after recurrence only palliative treatment suggested due to poor physical condition	Do	Do
16	68/F	Non-Hodgkin's lymphoma, metastasis to lung (small cell carcinoma), significant pleural effusion	January 2000	Patient refused chemotherapy due to poor health	Do	Do
17.	67/M	Renal cell carcinoma (September 1998), metastasis to lung and bone (February 2000)	1998	Surgical removal of the kidney in 1998 and palliative treatment suggested after recurrence	March 2000	Died, September 2000
18	75/M	Bronchogenic carcinoma with massive pleural effusion	—	Palliative treatment suggested	January 2000	Died, June 2000
19	55/F	Infiltrating duct carcinoma with metastasis to breast, lung and liver (July 1999) ascites in peritonium	July 1999	Surgery, radiotherapy and chemotherapy done with no response	March 2000	Died, May 2000
20	40/M	Infiltrating squamous cell carcinoma of larynx, metastasis to lymph gland	–	Surgery performed before	May 2000	Opted out, but patients condition was known to be good
21	55/M	Carcinoma of oesophagus	–	Only palliative treatment suggested	April 2000	Opted out, died
22	65/F	Metastatic adenocarcinoma of gall-bladder with involvement of liver and pancreas	April 2000	Choledochoduodenostomy was done, palliative treatment suggested	May 2000	Responded well, but opted out Oct 2000
23	78/M	Squamous cell carcinoma of cheek (3rd time relapse)	–	–	June 2000	Opted out, Sep 2000
24	50/F	Adenocarcinoma of pancreas-colangio-carcinoma, metastasis to liver, gall-bladder	February 2000	Palliative treatment suggested	March 2000	Response good, but opted out, died on May 2000

4. Discussion

The results of the present study appear to be very promising. Because, many of the patients who had volunteered for this study had metastatic carcinoma, received conventional treatment several times; however their conditions further deteriorated. There were many relapsed cases also, where the physicians who had treated previously thought of very poor prognosis what usually happens.

However it is remarkable to note that of the 19 patients who had continued with the present treatment, only 3 patients died. The conditions of other patients improved dramatically.

In the present context, some comments on the possible toxic effect of methylglyoxal seems worthwhile. It has been suggested for sometime by several investigators that methylglyoxal has both *in vitro* and *in vivo* toxic effects [13,14]. However, early studies by Apple and Greenberg and Szent-Györgyi *et al* had shown the methylglyoxal was well tolerated *in vivo* [2–5]. Moreover, the present study clearly indicates that in combination with other protective agents methylglyoxal has no major *in vivo* toxic effect. If at all there is any minor adverse effect, that is more than compensated by the apparent total control of malignancy.

In several previous publications from our laboratory, we had shown that methylglyoxal strongly inhibits the electron flow through complex I of the mitochondrial respiratory chain of specifically malignant cells. We had also shown that methylglyoxal specifically inactivates glyceraldehyde-3-phosphate dehydrogenas, the key enzyme of the glycolytic pathway. This is the only enzyme in the glycolytic pathway responsible for the production of NADH (reduced nicotinamide adenine dinucleotide). This NADH is subsequently oxidized through complex I. Almost 85% of the ATP generated in the cell are produced by the electron flow through complex I of the mitochondrial respiratory chain by the oxidation of NADH. Due to the inhibition of complex I and inactivation of the enzyme glyceraldehyde-3-phosphate dehydrogenase of specifically malignant cells by methylglyoxal these cells are devoid of ATP and hence the tumoricidal effect of methylglyoxal.

So, it appears that the underlying principle of the *in vitro* tumoricidal effect of methylglyoxal and of the destruction of specifically the malignant cells in patients is basically the same. The results of the above-mentioned study and the proposed mechanism of the tumoricidal effect of methylglyoxal strongly suggest that the present formulation is essentially the drug of choice for the treatment of cancer, although there is a vast scope for improvement of the formulation and also in treatment schedule. Moreover judicious medical supervision and support, and proper clinical monitoring of the patients' conditions are imperative.

We sincerely hope that researchers and clinicians with open mind will immediately make a concerted effort to use and to further improve the present formulation and treatment. Then and only then, this dreadful disease from which millions of people are suffering at present throughout the globe will be truly controlled.

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