IMPROVING CANCER RADIOThERAPY WITH 2-DEOXY-D-GLUCOSE:
PHASE I/II CLINICAL TRIALS ON HUMAN CEREBRAL GLIOMAS

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Purpose: Evaluation of tolerance, toxicity, and feasibility of combining large fraction (5 Gy) radiotherapy
with 2-deoxy-D-glucose (2DG), an inhibitor of glucose transport and glycolysis, which has been shown to
differentially inhibit repair of radiation damage in cancer cells.

Methods and Materials: Twenty patients with supratentorial glioma (Grade 3/4), following surgery were
treated with four weekly fractions of oral 2DG (200 mg/kg body weight) followed by whole brain irradiation
(5 Gy). Two weeks later, supplemental focal radiation to the tumor site (14 Gy/7 fractions) was given.
Routine clinical evaluation, x-ray computerized tomography (CT), and magnetic resonance (MR) imaging
were carried out to study the acute and late radiation effects.

Results: All the 20 patients completed the treatment without any interruption. The vital parameters were
within normal limits during the treatment. None reported headache during the treatment. Mild to moderate
nausea and vomiting were observed during the days of combined therapy (2DG + RT) in 10 patients. No
significant deterioration of the neurological status was observed during the treatment period. Seven patients
were alive at 63, 43, 36, 28, 27, 19, and 18 months of follow-up. In these patients, the clinical and MR
imaging studies also showed the absence of any brain parenchymal damage.

2-Deoxy-D-glucose, Cerebral gliomas, Radiotherapy.

INTRODUCTION

The prognosis of patients suffering from malignant cerebro-5mal gliomas has remained dismal despite application of
multimodal therapy and many advances in medical radiation
technology (1, 36, 51). The failure of radiotherapy in cerebral gliomas is primarily due to the presence of
hypoxic, intrinsically radioresistant, and repair proficient
subpopulations of cells in the tumor (36, 63, 64). Cerebral gliomas are heterogeneous tumors exhibiting large
variations in their genotype. DNA content, proliferation
kinetics, and metabolic and immunological status (6, 20,
52). Amplification in the expression of cellular oncogenes like ras, myc, and N-ras, known to confer radioresistance (37), has been demonstrated in gliomas (49).
An analysis of the pattern of failure after conventional
therapy comprising surgery, radiotherapy, and chemotherapy indicates local regrowth of the tumor to be the major contributor, implying that the conventional treatment (1.8–2.0 Gy/fraction; 30–35 fractions; five fractions/week; total absorbed dose 60–70 Gy) is inadequate in local control of the tumor (1). On the other hand, delivery of high radiation doses is limited due to damage to surrounding normal brain tissues (50). Therefore, it has been suggested that experimental approaches based on newer understanding of the biology of gliomas should be explored in Phase I/II clinical trials (5, 36). Strategies directed towards differentially enhancing radiation damage in tumor cells and reducing the damage to normal tissues could significantly improve the treatment efficacy of radiotherapy leading to better local control (28, 31, 46).

Experimental evidence suggests that damage to DNA is the major cause of cell death and cell loss induced by ionizing radiations in living organisms. A variety of DNA lesions are induced in cells exposed to ionizing radiations; most of these lesions (including double strand breaks) can be repaired by the various repair pathways. The biological end points such as cell death, mutations, and transformations are, thus, determined by competitions between the processes of error-free repair, misrepair, and fixation of DNA lesions (10, 30). Earlier studies have demonstrated that the cellular processes leading to the repair and fixation of radiation damage require continuous flow of metabolic energy (26, 30, 32, 43) supplied by the respiratory and/or the glycolytic pathways (32, 61). Because glucose usage in transformed cells and tumors is increased and tumor cells derive a large part of their metabolic energy (ATP) from the glycolytic pathway (62), it was predicted that inhibitors of glucose transport and glycolysis could differentially inhibit repair processes in these cells, leading to an enhancement of the radiation damage (32). Subsequent studies demonstrated that the presence of 2-deoxy-D-glucose (2DG), an inhibitor of glucose transport and glycolysis, during the first few hours following irradiation, could, indeed, inhibit the repair of DNA lesions and potentially lethal damage (PLD), thereby enhancing the radiation damage in various cellular systems with high rates of glycolysis like the cancer cells under euoxic as well as hypoxic conditions (18, 19, 27, 30, 34). Interestingly, under similar conditions, a decrease in radiation damage has been observed in normal cells (29, 31, 35, 54). Therefore, combination of ionizing radiations with 2DG provides a unique opportunity to selectively destroy tumors by differentially enhancing the radiation damage in cancer cells and at the same time preventing radiation injuries to normal tissues. Experiments on animal tumor models have provided support for this suggestion (33, 48).

Human cerebral gliomas appear to be most appropriate to verify the validity of this approach, because studies using positron emission tomography (PET) have shown that 18F-deoxy-o-glucose accumulates in most of the cerebral gliomas and its accumulation correlates with the degree of malignancy (16). Glioma cells in vitro have also been observed to manifest high rates of glucose usage and glycolysis (60). Investigations on a cell line derived from a human cerebral glioma showed that energy linked inhibition of DNA repair and modulation of cell proliferation due to the presence of 2DG, could lead to an increase in the radiation-induced micronuclei formation (18, 19). Studies on organ cultures using explants derived from human cerebral gliomas showed that the presence of 2DG for a few hours after irradiation could increase the frequency of micronuclei formation in most cases (17). Therefore, it may be expected that combining 2DG with radiation would significantly enhance the efficacy of radiotherapy of cerebral gliomas. In the present studies, irradiation with large dose fractions was considered necessary to achieve significant and effective 2DG-induced inhibition of PLD repair in tumor cells, repair ratio being proportional to absorbed dose in this range (25). The treatment regimen was designed, for the sake of convenience and safety, to combine 2DG with weekly fractionation of 5 Gy because the use of conventional radiotherapy would entail daily administration and monitoring of 2DG. Furthermore, this altered treatment regimen would also minimize the 2DG requirement and reduce the machine time required for delivery of radiation dose. The major objectives of the present investigations were to examine the feasibility of administering oral 2DG with high dose per fraction (5 Gy) of 60Co gamma radiation and to evaluate the tolerance and toxicity of this combined therapy in a population of supratentorial high grade gliomas. Preliminary results of this work have been presented (44).

**METHODS AND MATERIALS**

**Authorization**

The present studies were conducted after clearance from the ethics committees of KMIO, Bangalore and AIIMS, New Delhi. Approval of the Drug Controller, Ministry of Health and Family Welfare, in India was also obtained.

**Patients**

Twenty patients (15 males, 5 females), in the age group of 21–64 years with supratentorial malignant gliomas (Karnofsky performance status score > 70) were included in the present study after informed consent. They were treated between October 1988 and June 1992 at KMIO (10 patients) and at Institute Rotary Cancer Hospital, AIIMS (10 patients). Routine pretreatment investigations included complete hemogram, renal and liver function tests, and contrast enhanced CT scan of the brain besides neurological examination. Diagnosis and grading of the tumor were confirmed on the basis of histopathological investigations according to the WHO criteria (66). Surgery was carried out to achieve adequate tumor excision (decompression in 14 and near total excision in 6 patients). Tumor volume was also measured with the help of CT scan (38) before and after surgery in the 10 patients...
Improving cancer radiotherapy with 2-deoxy-D-glucose • B. K. Mohanti et al.

Table 1. Grade 3 gliomas: Patients, tumor characteristics, treatment and survival (n = 4)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Age/Sex</th>
<th>Site</th>
<th>Surgery date</th>
<th>Tumor vol (ml)</th>
<th>Survival (months)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. K1</td>
<td>28/M</td>
<td>Lt. Frontal</td>
<td>NTE 9/30/88</td>
<td>44</td>
<td>&gt;63</td>
<td>Recurrence at 38 months (lost to follow-up)</td>
</tr>
<tr>
<td>2. K2</td>
<td>59/M</td>
<td>Lt. Temporal</td>
<td>Decomp. 1/18/88</td>
<td>61</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3. K6</td>
<td>40/M</td>
<td>Lt. Frontal</td>
<td>NTE 6/5/90</td>
<td>37</td>
<td>&gt;43</td>
<td>Alive, Disease free</td>
</tr>
<tr>
<td>4. K8</td>
<td>36/M</td>
<td>Lt. Parietal</td>
<td>Decomp. 9/19/91</td>
<td>63</td>
<td>&gt;27</td>
<td>Alive, with disease</td>
</tr>
</tbody>
</table>

Lt. = Left; NTE = near total excision; Decomp. = decompression of tumor.
* Volume assessed from CT scans.
1 Measurements made 2 to 3 weeks after the fourth fraction of 2-DG + RT.
1 Institute-wise serial no. of the patients. K = KMIO, Bangalore.

Blood samples were collected hourly up to 6 h following 2DG administration and at 24 h to estimate 2DG and glucose levels. Glucose was estimated by the reducing sugar method (55) and 2DG using the diaminobenzoic acid (DABA) assay (7).

Follow-up

All patients were evaluated periodically (every 3–6 months) with clinical assessment, CT scan, and MR imaging. These patients were followed until September 1994 or death.

MR imaging

Fifteen patients underwent one or more MR examinations from 2–60 months after radiotherapy. Noncontrast MRI of the brain was carried out using a whole-body superconducting tomograph1 with the help of a standard head coil. Using T1 (TR 700 ms/TE 17–22 ms) and T2 (TR 1.8 s/TE 90 ms) spin echo sequences in an axial plane, 5 mm slices with 50% interslice gap were acquired (matrix size 256 × 256). Additional multiecho (eight echoes) sequences were taken for calculating relaxation time T2 with the help of standard software. Occasionally, coronal plane images were also taken to clearly define the extent of tumor.

RESULTS

A brief summary of the clinical and survival data for all the 20 patients (4 with Grade 3 and 16 with Grade 4 tumors) is presented in Tables 1 and 2. Though the protocol was designed for accrual of the patients with malignant gliomas, four of the treated patients had Grade 3 lesions. The pathologic grades in all the 20 patients were reviewed by one of the coauthors (S.D.). In the KMIO series, the postsurgical tumor volumes evaluated before administering the treatment varied from 15 to 167 ml (Tables 1 and 2, K1–K10).

Acute effects. No significant change in any of the vital parameters was noticed either on the day of treatment or on subsequent days (Table 3). However, general weak-

1 Theratron 780-C, AECL, Canada.
2 Magnetom, GBS 1, Siemens, Germany.
Table 2. Grade 4 gliomas: Patients, tumor characteristics, treatment and survival (n = 16)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Age/Sex</th>
<th>Site</th>
<th>Surgery date</th>
<th>Tumor Vol. (ml)*</th>
<th>Pre-Rx</th>
<th>Post-Rx+ (months)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>K3°</td>
<td>43/M</td>
<td>Rt. temporoparietal</td>
<td>Decomp. 2/18/89</td>
<td>127</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>2.</td>
<td>K4</td>
<td>62/M</td>
<td>Rt. temporal</td>
<td>NTE 4/30/90</td>
<td>70°</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>3.</td>
<td>K5</td>
<td>34/M</td>
<td>Rt. temporal</td>
<td>Decomp. 6/5/90</td>
<td>15</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>4.</td>
<td>K7</td>
<td>26/F</td>
<td>Rt. parietal</td>
<td>Decomp. 8/3/90</td>
<td>20</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>5.</td>
<td>K9</td>
<td>36/M</td>
<td>Lt. temporal</td>
<td>NTE 1/2/92</td>
<td>34</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>7.</td>
<td>A1</td>
<td>52/M</td>
<td>Rt. temporoparietal</td>
<td>Decomp. 1/10/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>A2</td>
<td>55/F</td>
<td>Rt. frontal</td>
<td>NTE 1/3/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>A3</td>
<td>21/F</td>
<td>Rt. frontal</td>
<td>Decomp. 3/28/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>A4</td>
<td>32/F</td>
<td>Rt. frontal</td>
<td>Decomp. 4/4/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>A5</td>
<td>40/M</td>
<td>Rt. temporal</td>
<td>Decomp. 5/1/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>A6</td>
<td>64/M</td>
<td>Lt. parietal</td>
<td>NTE 4/4/91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>A7</td>
<td>55/M</td>
<td>Lt. temporoparietal</td>
<td>Decomp. 9/9/91</td>
<td></td>
<td></td>
<td>&gt;19 Lost to follow-up</td>
</tr>
<tr>
<td>14.</td>
<td>A8</td>
<td>64/F</td>
<td>Lt. frontoparietal</td>
<td>Decomp. 12/4/91</td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>15.</td>
<td>A9</td>
<td>48/M</td>
<td>Lt. frontoparietal</td>
<td>Decomp. 12/5/91</td>
<td></td>
<td></td>
<td>36 Recurrence at 19 months</td>
</tr>
<tr>
<td>16.</td>
<td>A10</td>
<td>35/M</td>
<td>Lt. frontal</td>
<td>Decomp. 1/8/92</td>
<td></td>
<td></td>
<td>28 Disease free</td>
</tr>
</tbody>
</table>

Lt. = Left; Rt. = right; NTE = near total excision; Decomp. = decompression of tumor.

* Volume assessed from CT scans.

° Measurements made 2 to 3 weeks after the fourth fraction of 2-DG + RT.

° Institution-wise serial number of the patients; K = KMIO, Bangalore; A = AIIMS, New Delhi.

° Presurgical volume.

ness and lethargy was prominent in all patients on the day of administering the combined (2DG + RT) treatment. Nausea and vomiting were absent in 10, mild in 3, and moderate in 7 patients, and lasted for nearly 18–24 h after 2DG administration. All patients were treated with i.v. fluids, metochlopropamide, and antiedema measures like mannitol and lasix. Steroids were used in only two patients. Sweating was observed in nine patients. However, the peripheral pulse rate and the blood pressure remained stable in all 20 patients. Appetite was poor on treatment days, but it was normal during the rest of the therapy. Headache was not reported by any of the patients during the course of the treatment. Hemogram and blood urea levels measured weekly were within normal limits in all of the patients.

In all 20 patients, blood 2DG levels showed a maximum at 1 h after administration and thereafter decreased exponentially with an average half life of 89 ± 17 min.

Table 3. Acute effects observed in patients treated with the combined (2-DG + RT) protocol

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>Stable</td>
<td>Moderate</td>
<td>1 episode</td>
<td>Stable</td>
<td>Drowsy</td>
</tr>
<tr>
<td>K2</td>
<td>Stable</td>
<td>Mild</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K3</td>
<td>Low</td>
<td>Moderate</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K4</td>
<td>Stable</td>
<td>Nil</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K5</td>
<td>Low</td>
<td>Nil</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K6</td>
<td>Low</td>
<td>Moderate</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K7</td>
<td>Stable</td>
<td>Moderate</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K8</td>
<td>Stable</td>
<td>Moderate</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K9</td>
<td>Stable</td>
<td>Nil</td>
<td>Nil</td>
<td>Stable</td>
<td>Alert</td>
</tr>
<tr>
<td>K10</td>
<td>Stable</td>
<td>Nil</td>
<td>Nil</td>
<td>Stable</td>
<td>Drowsy &amp; Giddiness</td>
</tr>
<tr>
<td>A1</td>
<td>Stable</td>
<td>Nil</td>
<td>Nil</td>
<td>Stable</td>
<td>Giddy</td>
</tr>
<tr>
<td>A2</td>
<td>Stable</td>
<td>Nil</td>
<td>Once</td>
<td>Stable</td>
<td>Drowsy</td>
</tr>
<tr>
<td>A3</td>
<td>Stable</td>
<td>Moderate</td>
<td>Nil</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>A4</td>
<td>Stable</td>
<td>Nil</td>
<td>Once</td>
<td>Stable</td>
<td>Seizure once</td>
</tr>
<tr>
<td>A5</td>
<td>Low</td>
<td>Nil</td>
<td>Once</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>A6</td>
<td>Low</td>
<td>Nil</td>
<td>Severe</td>
<td>Stable</td>
<td>Drowsy</td>
</tr>
<tr>
<td>A7</td>
<td>Low</td>
<td>Nil</td>
<td>Severe</td>
<td>Stable</td>
<td>Drowsy</td>
</tr>
<tr>
<td>A8</td>
<td>Stable</td>
<td>Moderate</td>
<td>&gt;2 times</td>
<td>Stable</td>
<td>Disorientation</td>
</tr>
<tr>
<td>A9</td>
<td>Stable</td>
<td>Mild</td>
<td>&gt;2 times</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>A10</td>
<td>Stable</td>
<td>Nil</td>
<td>Once</td>
<td>Stable</td>
<td>Drowsy</td>
</tr>
</tbody>
</table>

* Institution-wise serial no. of the patients; K: KMIO, Bangalore; A: AIIMS, New Delhi.
Improving cancer radiotherapy with 2-deoxy-D-glucose

The levels of glucose, 2DG, and the molar concentration ratio (2DG/G) observed in a typical case are presented in Fig. 1. By 24 h, detectable amounts of 2DG were not found in the blood. Blood glucose levels gradually increased following 2DG administration, reaching a maximum value (three to four times the basal level of 5.0 ± 0.8 mM) at about 3 h after administration. The levels subsequently decreased and reached the basal value by 24 h. The ratio of 2DG to glucose in the blood was found to be the highest (0.6–1.0) 1 h after 2DG administration and decreased rapidly reaching an insignificant value (< 0.02) by 6 h.

None of the patients developed any new neurological deficit during the entire period of therapy. In five patients, the general condition and the neurological status showed significant improvement at the end of therapy. At the completion of the planned protocol, in the KM10 series, the tumor volume decreased in eight patients, while an increase was observed in the remaining two patients.

Late effects

The median survival in this study was 13 months and 7 patients (35%) were alive at 63, 43, 36, 28, 27, 19, and 18 months of follow-up (Tables 1 and 2). Three of these seven patients were lost to follow-up at 63, 19, and 18 months. The median survival was 32 months in the four patients with Grade 3 tumors, whereas it was observed to be 13 months in the 16 patients with Grade 4 gliomas. However, the number of patients with Grade 3 lesions is too small (four patients) for any meaningful inference.

Five patients had recurrence at the primary site and three of these were subjected to salvage therapy (one underwent surgical decompression and the other two received four courses of oral nitrosourea). These three salvaged patients were alive at 63, 36, and 28 months. The remaining two patients succumbed to the disease at 10 and 11 months.

The MR imaging was carried out to evaluate the late radiation effects in seven patients between 12 and 60 months after the therapy. Representative MR images of a 48-year-old patient investigated at 6 and 18 months of follow-up are given in Fig. 2. Periventricular hyperintensity patterns were graded, as described by Constine et al., based on Zimmerman’s classification (11,65). Of the seven patients, four did not show any white matter changes indicating the absence of late radiation damage (Table 4), while in three others, Constine’s Grade 1 to 3 changes were observed.

None of the living patients showed any clinical features of late radiation encephalopathy till their last follow-up evaluation. None of the living patients had any higher motor function impairment.

DISCUSSION

Although the role of external radiation therapy in modestly prolonging survival following primary surgery has been clearly demonstrated (23), the current practice of conventional fractionation or hyperfractionation has not provided any significant overall benefit in the management of gliomas (13, 15, 25). The radioresistance of these tumors (primarily responsible for the failure of radiotherapy) could be due to efficient defense, the repair and repopulation mechanisms in the glioma cells, or to radioprotection afforded by the microenvironment. Results of in vitro studies have shown that glioma cells are proficient in the repair of potentially lethal damage (13, 15). The SF2 values (0.4–0.73) reported for many of the glioma cell lines and primary cultures (2, 58) also point to the radioresistant nature of glioma cells requiring high radiation dose (> 2 Gy) to overcome the shoulder (21). To achieve significant cell kill and to improve the therapeutic outcome, a few promising attempts to use large fraction irradiation have been made (24, 59).

The need to develop strategies based on biology of the
tumor cells that enhance cell kill, while reducing radiation damage to the normal brain, is being increasingly realized. The present approach, which is based on energy-linked modifications of repair and fixation processes through the combination of 2DG with low LET radiations, is an attempt in this direction (31, 32). The present study demonstrates that the combination of 2DG (200 mg/kg body weight) with large doses of gamma-irradiation (4 × 5 Gy/fraction/week) is feasible and causes no serious side effects.

2DG is transported across the blood–brain barrier by mechanisms similar to those for glucose, and phosphorylated by hexokinase to 2-deoxy-D-glucose-6-phosphate (2DG-6-P), which accumulates in the tumor and blocks the glycolytic pathway (3). In the peripheral blood, maximum values of 2DG/G ratios (0.6 to 1.0) were observed 1 h after oral administration of 2DG. If our hypothesis suggesting 2DG-induced differential inhibition of DNA repair in tumor cells is valid, high levels of 2DG in the tumor would be required only for short intervals of time following irradiation (the time constant of DNA repair processes in human cells being less than 1 h). It is expected that 2DG-6-P in adequate amounts would be present in tumor cells under these conditions. In the present studies, estimates of 2DG or 2DG-6-P levels in the tumors could not be made; however, measurements of 2DG-6-P using magnetic resonance (MR) spectroscopy or PET are planned in subsequent studies.

The major concern in the present studies has been about the acute physiological changes induced by the administration of 2DG. Perturbations are caused by the inhibition of glucose usage (cellular glucopenia), particularly in the functioning of neuroendocrinal system in the presence of 2DG. The observed hyperglycemic state may be caused partly by the increased secretion of noradrenalin from the hypothalamus leading to the release of glucagon from the

Table 4. Late radiation effects in patients treated with the combined protocol evaluated from white matter changes (Constine’s grading of periventricular hyperintensity) investigated using MRI

<table>
<thead>
<tr>
<th>Pt. No.*</th>
<th>Age/sex</th>
<th>Follow-up time (months)</th>
<th>Periventricular hyperintensity (Constine’s grading)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1</td>
<td>28/M</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>K6</td>
<td>40/M</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>A3</td>
<td>21/F</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>A6</td>
<td>64/M</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>A7</td>
<td>55/M</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>A9</td>
<td>48/M</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>A10</td>
<td>35/M</td>
<td>4</td>
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* Institution-wise serial no. of patients; K: KMIO, Bangalore; A: AIIMS, New Delhi.
pancreas, mobilization of fatty acids, breakdown of liver glycogen and gluconeogenesis (39). This may, possibly, cause nausea and vomiting as observed earlier (45). In this study, 9 out of 20 patients experienced a mild to moderate degree of nausea and vomiting (Table 3). However, these symptoms did not call for interruption of treatment, and the patient compliance was satisfactory. Eight patients showed features of drowsiness or stated giddiness, that lasted for a period of 4–5 h, on the days of combined treatment. Only one patient suffered from seizure on 1 of the 4 days of treatment (Table 3).

Clinical signs and symptoms of increased neurological deficits were not observed in any of the patients, and considerable improvement was noticed in 25% of the cases during the course of therapy. Headache has been reported as a common symptom after irradiation with higher dose fractions (57). This problem was not encountered in the present study.

Brain is a classic late-responding tissue to radiation. For the development of radiation myelitis, besides the cytokinetic organization, other important factors are the total radiation dose, dose per fraction, the repair kinetics, and repair capacities of the tissues. The currently available information on these parameters in normal brain and gliomas is insufficient to suggest optimal radiotherapy regimens. Although, the safe daily fraction size in the treatment of brain tumors is recommended to be 1.8–1.9 Gy (47), no neural tissue damage (clinical or histologically) has been observed with a dose of 4 33 Gy and misonidazole (8). On the other hand, a few studies with large dose fraction radiotherapy using 4–5 Gy/fraction have indicated some benefit with this schedule in the case of patients with glioblastoma multiforme (24, 59). The role of large fraction radiotherapy in the treatment of brain tumors, therefore, needs to be examined further.

It is interesting to note that in the seven living patients of the present series, clinical features of late radiation neuropathy were not observed, inspite of a high dose per fraction of 5 Gy and a total observed dose equivalent to the conventional total RT dose of 55 Gy (4, 53). The development of late radiation damage in brain, often leading to radiation necrosis, shows a steep dose response from essentially no effect to full effect beyond a critical threshold dose (22). Further, Sheline (53) observed that brain necrosis occurred in patients who received doses corresponding to a range of 1700 to 1800 ret and neurset doses of 1000 to 1100. There has been some apprehension that a high dose per fraction could lead to greater late effects in the central nervous system (14), mainly in the form of demyelinating lesions with focal or diffuse areas of white matter necrosis (9). Magnetic resonance imaging has been shown to identify these lesions with greater sensitivity due to alterations in water content accompanying these lesions (11, 12). Five periventricular patterns or grades of increasing extent and intensity have been identified, and higher grade lesions were associated with radiation to large volumes and high dose (11, 65). MRI evaluation in seven of our patients during the follow-up revealed Constatine’s Grade 0–1 changes in 4 and Grade 1–3 changes in three patients. Present observations could be either due to lower whole brain radiation of 20 Gy in 4 fractions (equivalent to conventional schedule of 41 Gy; 905 neutrons) and/or a possible protective effect of 2DG on the glial cells of white matter and endothelial cells of the vasculature, the two important targets of late radiation damage (4, 12, 41, 42). These possibilities are of significance for the study of damage to brain parenchyma vis-a-vis large fractionated therapy, and they need to be investigated in detail using more advanced and sensitive techniques.

In conclusion, present studies show that all the patients could well tolerate the combined treatment of 2DG with large dose per fraction (5 Gy). Although, the objectives of this study were to evaluate the tolerance, toxicity, and feasibility of this experimental protocol, the median survival of 13 months observed in the 20 patients compares well with the published values (13, 24, 51). Therefore, further clinical trials to determine the optimal dose of both 2DG and radiation in escalating dose schedules and to evaluate the efficacy of this treatment are warranted. Although at this stage, it is understood that the presence of 2DG enhances the effects of irradiation in the glioma cells (17), future human studies should also be designed to observe the separate effects of large dose per fraction of radiotherapy and the oral intake of 2DG.

REFERENCES

Improving cancer radiotherapy with 2-deoxy-D-glucose • B. K. Mohanti et al.


