Nutritional Support and Prognosis of Patients with Astrocytoma Grades Three or Four: A Prospective Pilot-Study

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Abstract

Seventeen patients with mostly inoperable astrocytoma grade 3 or 4, received nutritional therapy and were compared to three groups of patients, being younger and more exposed to operation and irradiation. In spite of the higher abundance of negative prognostic factors, median survival of the nutritionally treated group was 18 months and ten days. After one year there were significantly more patients alive in this group, compared with the other three groups. This was a prospective research.

Keywords: Astrocytoma 3 and/or 4; orthomolecular therapy/nutrition; clinical epidemiology; prospective.

Introduction

Astrocytoma grades 3 or 4 are malignancies with a poor prognosis. Andersen found, after operation, a median survival of 4.5 months for astrocytoma grade 4; with supporting radiotherapy median survival was 7.5 months. The difference was statistically significant.[1] In the same way Walker *et al*[2] and Kristiansen *et al*[3] found prolongation of life by postoperative radiotherapy with patients suffering from astrocytoma grades 3 or 4; they had mixed populations of both astrocytomas. Median survival with only surgery was respectively 3.5 and 5.2 months; with supporting radiotherapy median survival was respectively 8.7 and 10.8 months. Surgery alone has never been compared with mere symptomatic treatment (prednisone etc.). It is clear however, that surgery correlates with a better survival.[2]

Chemotherapy has very modest possibilities in these astrocytomas. Walker[2] found a median survival of 14 weeks with surgery alone. With BCNU (1.3-bis(2 chloroethyl)-1-nitrosourea) median survival was 18.5 weeks (the difference was statistically significant). When radiotherapy and BCNU-treatment were both applied, median survival was not significantly better than with radiotherapy as the only supporting treatment (median survival was respectively 35 and 34.5 weeks although average survival was best in the group that received radiotherapy and BCNU; but this was not statistically significant either).

In a placebo controlled study, intravenously administered bleomycin did not potentiate the effect of supporting radiotherapy with patients suffering from astrocytoma grades 3 or 4.[3] Shin et al[4] found no significant prolongation of life when radiotherapy and misonidazole were compared with radiotherapy as the only supporting therapy.

Prognostic factors are:

a) Histological gradation: patients with astrocytoma grade 4 have a worse prognosis than patients with an astrocytoma grade 3.[5]

b) A low Karnofsky-index significantly correlates with a bad prognosis.[2]

c) Older people have, in general, a significantly worse prognosis than younger people.[1,6] Andersen[1] found that patients over 60 years old have a significantly worse prognosis than patients younger than 60. Yonoyama et al[6] found that patients over 36 years old have a worse prognosis than patients under 36. However, Yonoyama also found that the group under 15 years old had a significantly worse prognosis

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compared with the rest of the sub-36 group and also when compared with the patients of over 36. So the group 16-35 years has the best prognosis. Although it is very likely that surgery prolongs life, the extent of surgery does not significantly influence survival.[5] Duration of symptoms bears an inverse relationship to survival, which is especially significant for patients that had symptoms longer than six months before diagnosis. They lived significantly longer than the rest.[6] Location is another important prognostic factor. None of the patients in the patient group of Yonoyama,[6] with a deep or bilateral astrocytoma grade 3 or 4, survived after radiation therapy. In the same group, patients with a right-sided tumour had a more favourable prognosis than those with a left-sided tumour; the survival of these two groups was statistically different at two and three years after treatment. A right frontal location yielded a significantly better survival after two, three, four and five years compared with tumours located in the left frontal or in any other lobe. The favourable prognosis of the right-sided tumours is entirely attributable to the tumours located right frontally. Nutritional factors are very important in the prevention of cancer. More and more evidence is accumulating that most substances that prevent cancer also retard progression of existing cancer or even can cure it.[7-10] With special reference to astrocytoma, extra vitamin C during pregnancy seems to reduce the risk of astrocytoma in the offspring.[11]

Much is unknown about possible therapeutic effects of nutrition. The following facts are interesting. The herb Pao Pareira inhibits, according to very recent research, the growth of an astrocytoma grade 3 in vitro up to 100 percent.[12] Amygdalin (a form of vitamin B17) might cause regression in astrocytoma grade 3 and 4 according to Dutch and German physicians.[13] Phenylacetate, a metabolite of phenylalanine, induces differentiation in gliosarcomas and this is at least one reason that phenylacetate prolongs life in rats implanted with this kind of tumour.[14] Malignant glioma cells also differentiate in vitro, when phenylacetate is administered .[15] Most nutrients discussed in references 7 to 10 have not been subjects of research in relation to astrocytomas. Nutritional support of patients with astrocytoma 3 or 4 is the subject of this study.

Patients and Methods.

The patient characteristics are summarized in **Table 1**(page 52).

The Diet Recommended

The diet recommended was based upon the so called Moerman-diet;[16] many details are discussed in reference 7. The following main guidelines can be given:

a) As much fruit and as many vegetables and/or juices derived from these as possible. Especially citrus fruits, pineapple, carrots, broccoli and spinach were recommended.

b) Brown rice and leguminous plants (later on especially soy products) are highly preferable over potatoes.

c) Fat fish (not smoked) was advised three times a week. Herring, salmon, mackerel, tuna and sea-devil were especially recommended.

d)Leavened bread made from wheat and/or rye without extra fat was recommended.

e) Milk-products: only low fat milk-products, containing living lactobacilli, were permitted to a maximum of 0.5 litre a day.

f) Cheese: only young cheese and no more than 40 grams daily.

g) No meat

h) Nuts and seeds: walnuts, almonds, pumpkinseed, sesameseed and linseed. Walnuts and almonds are preferred to other nuts, because of their high content of omega-3 fatty acids. Maize and peanuts were discouraged.

i) Mushrooms: only Shiitake-mushrooms were recommended.

j) Oils and fats: for heating, only olive oil was recommended. For salads linseed oil,

Table 1: Characteristics of the patients; treatment refers to standard treatment; (10A and 10B are one patient).

patient	sex	age	grade	location	treatment	delay
1	F	68	4	unknown	operation + radiation	unknown
2	M	26	4	brain	radiation	11.5 weeks
3	M	35	4	left parietotemporal	radiation + canula	16 weeks
4	F	34	3, pilocytic	right deep temporal up to medial line	inoperable, radiation + after relapse, operation	<3 months
5	F	27	4	left frontal	biopsy	1 month
6	M	36	3/4	unknown	debulking + radiation	unknown
7	F	27	3	unknown	operation	not clear; 2.5 years before grade 2
8	M	34	4	right parietotemporal	operation + radiation	3-4 months
9	M	51	4	right parietooccipital	2 operations + after radiation	4 weeks
10a	M	60	3	left frontal	biopsy + radiation	19-30 months
10b	M	62	4	left frontal	operation	4-5 months
11	M	31	3	right temporal	debulking, radiation, reoperation	5-6 years
12	M	47	3, pilocytic	right frontal	operation + radiation	unknown
13	M	43	4	right parietotemporal	operation, radiation	6 weeks
14	F	41	4	right frontoparietal	operation, radiation brachytherapy	10 days
15	M	37	3	brain stem	radiation	5 months
16	F	27	3	left parietal	operation + radiation	1 year
17	F	46	4	right frontal	biopsy + debulking radiation + reoperation	4 months

soybean oil, walnut oil and/or pumpkin-seed oil were recommended. The use of corn oil, sunflower oil and safflower oil was discouraged. Only a minimal amount of butter (on bread) was allowed.

k) Herbs and spices: garlic, caraway seed, saffron, rosemary and curcuma were especially recommended. Parsley, ginger and capsicum were recommended to a lesser extent. Redundant salt was discouraged.

l) Sugar: no (white) sugar; only minimal honey.

m) Drinks: green tea and licorice tea were recommended; black tea was discouraged. One or two cups of regular coffee a day were allowed. The only alcohol allowed was several glasses of dry red wine a week.

Nutritional Supplementation

The following lists the nutrient composition of multivitamin/mineral combinations used. A summary of the nutrients used by each patient is shown in **Table 2**a (page 53) and **Table 2b** (page 54).

1) Composition of *Lamberts' "One Daily"* vitamins and minerals (per tablet) is as follows:

vitamin A	3.996 IU
beta-carotene	3330 IU
vitamin D	200 IU
vitamin E	100 IU
vitamin C	150 mg

vitamin B_1	25 mg
vitamin B_2	25 mg
niacin	100 mg
vitamin B_6	25 mg
folic acid	400 mcg
vitamin B_{12}	10.0 mcg
biotin	0.15 mg
pantothenic acid	50 mg
choline	25 mg
inositol	25 mg
PABA	25 mg
dicalcium phosphate	75 mg
ferro fumarate	10 mg
zinc gluconate	15 mg
potassium iodide	150 mcg
manganese gluconate	5 mg
copper gluconate	2 mg
molybdate	500 mcg
seleno-l-methionine	200 mcg
chromium (AA chelate)	200 mcg

(all minerals and trace elements are expressed in elemental values).

2) Composition of *"Dagravit 30 Totaal"* per tablet is as follows:

vitamin A	0.3 mg
vitamin B_1	1.5 mg
vitamin B_2	1.5 mg
vitamin B_6	0.5 mg
vitamin B_{12}	0.5 mcg
niacin	10 mg
calcium d-pantothenate	1.5 mg
biotin	12.5 mcg
PABA	10 mg
vitamin C	20 mg
vitamin D_3	10 mcg
vitamin E	1 mg
rutin	2.5 mg
iron	15 mg
calciumphosphate	250 mg

Table 2a. Nutritional Supplementation of the Patient Group.

patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Supplement per Day																	
"One Daily" vitamins + minerals		1			1	1	1	1	1	1	1	1	1	1	1	1	1
"Dagravit 30 totaal"	2		1	1													
vitamin E (IU)	100	300	150	200	200	400	200	200	200	200	200	200	100	100	400	200	200
carotene (mg)	50	110		90		150		100	100	120	80	75	90	120	120	120	140
vitamin A (1000 IU)			45	75													
ascorbic acid (gr)	1	3	4.5	4.5	3				1.5		1.5	3	1.5	2	0.5	1.5	1.5
l-glutathione complex (# of 500 mg capsules)		1	1		1	1											
l-seleno-methionine (100 mcg)	5	5	5	10		14						8		4			
sodium selenite (1000 mcg)			3-4		1	1-2			1-4	1-4		1		1			
sulfur depuratum (0.5 gr)	1		2	1									0.5	1			
folic acid (mg)											5		5	5	5	5	5
ferro ascorbate (mg)	15	15															
ferri aromatica triplex; (mg Fe)			30			30					30						
SFB-complex					1	1						1					
Coenzyme Q10 (mg)													15				
cod liver oil (ml)						22		30	30	15		15	7	15		15	
polyerga; (# of tablets)		3															

potassium	5 mg
magnesium	5 mg
copper	0.5 mg
manganese	0.5 mg
zinc	0.5 mg
iodine	50 mcg
molybdenum	50 mcg
fluoride	50 mcg
nickel	50 mcg
selenium	50 mcg

Nutrients in these multivitamins are not added to the amount of the individual nutrients, given separately or in other combinations:

3) Glutathione-complex 500 mg consists of:

l-glutathione	50 mg
l-glutamic acid	194 mg
l-cysteine	158 mg
glycine	98 mg.

4) Ferri-aromatica-triplex was a solution with sucrose and Fe 3^{+} originally prescribed by the late physician, Moerman.[17]

5) SFB-complex contains per tablet:

coenzyme Q10	5 mg
thioctic acid	10 mg
vitamin E	100 mg
pyridoxal-5-phosphate	10 mg
vitamin B_1	10 mg
riboflavin (active form)	4 mg
niacin	40 mg
pantothenic acid	150 mg
magnesium citrate	210 mg

6) Polyerga is derived from embryonal Kupffer-cells of the liver.[17]

7) *Iscador* is an extract of the mistletoe.[18]

8) *Venalot* contains 15 mg coumarin and 90 mg troxerutin per tablet.

9) *Pao Pareira specific extract* (pareirine), is derived from the inner bark of a tropical tree.[19]

Table 2b. Nutritional Supplementation of the Patient Group.

patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Supplement per Day																	
Iscador in drops per day from Monday till Saturday										30					30	30	30
spirulina (# of 500 mg tablets)				1		6			2	3	3	2	3-5		3	3	1-3
Venolot (# of tablets)		3-6		2		3-7	6	3	3	3		2-6		2			
thymus extract: (# of 300 mg tablets)			3			3			2-4	1	2-3		2	2-5	5		
amygdalin (100 mg per day)			12	6		9			10	10	10	8	5	5	14	10	10
bitter almonds											9	6	10				
apricot kernels				15	3-36		30				4-9						
shitake extract (250 mg tablets)					2												
pycnogenol (50 mg tablets)						3-4	2	2	2-3	2-3							2
Peo Parei 300 mg containing (30% pareirine)															1-3	3-4	
magnesium, mainly as oxide: (400 mg per tablet)															1		
iodine (mg per day)				0.9													
bromelain (100 mg tablets)															3		
citrus bioflavonoids (500 mg tab)																	3

Results and Discussion.

The results are summarized in **Table 3**. Patient no. 3 developed a hemiplegia in spite of his corticosteroids and the canula. After the introduction of amygdalin the hemiplegia disappeared; the intake of the corticosteroids could be lowered and the regression was confirmed by a CT-scan. Patient 15 had an astrocytoma grade 3 of the brain stem. A decompression operation was only possible, followed by radiation treatment. His situation then slightly improved. Six months later, when he came under my treatment, he was still in a wheelchair. After half a year under my treatment he was somewhat better. Later on (between 9 and 20 months after radiation treatment) he continued to improve; he did not need the wheelchair any longer and was able to resume work. Two years after diagnosis his situation deteriorated and he died a few months later. It is clear that the regression of the tumour of patient no. 3 is not attributable to anything else but amygdalin.

In the case of patient no. 15 it is unlikely that the regression was due to a late effect of radiation treatment, because at first there was only some improvement of the situation, while the regression that I saw occurred a relatively long time after the decompression operation and radiation treatment. A spontaneous regression is not a likely explanation, because it has been

Table 3: Survival of Patient Group in Detail

patient	survival	remarks
1	1 year, 7 months, 23 days	nutritional support first started after approximately 1 year of disease
2	one year, a few days	
3	3 years, 8 months, 2 weeks	partial regression during nutrition therapy
4	7 years, 9 months, 1 week, 5 days; still alive	
5	10 weeks	
6	1 year, 1 month, 1 day	
7	6 months, 2 weeks, 1 day	had an astrocytoma grade 2, 31 months before diagnosis grade 3
8	9 months, 4 days	bad compliance with therapy
9	1 year, 11 days	
10	2 years, 7 months, 1 week	1 year and 10.5 months after the initial diagnosis astrocytoma grade 3, the cancer had developed into an astrocytoma grade 4
11	5 years, 3 months, 1 week; alive	partial regression during nutritional therapy
12	1 year, 6 months, 17 days	started nutritional therapy first after 14 months
13	1 year, 2 days	
14	16 months, 3 weeks, 5 days	received radiotherapy partially as brachytherapy
15	2 years, 4 month, 2 days	
16	3 years, 1 month, 5 days; still alive	
17	1 year, 1 month	

seen only once in the case of a patient with an astrocytoma grade 3, which was partly operable. An infection caused a regression of the remaining tumour, after 18 months there was a relapse.[20]

Patient no. 3 had an astrocytoma grade 4 and patient 15 had a brain stem astrocytoma grade 3; both were inoperable and during the clinical course there were no infections. So especially these two patients were very remarkable.

Moerman himself treated with a less extensive but comparable regime of diet and supplements, a ten-year old boy who suffered from a relapse of an astrocytoma grade 4, which had been treated 3 months earlier with operation and radiation treatment. The boy recovered and almost 25 years later he is still in good health.[16]

The average age of the patient group at diagnosis was 40.5 years; median age was 37 years. Compared with research on similar patients in hospitals in Europe, the U.S.A. and Australia, our patients are, on average, younger. The average age of the patients in the references 1, 2, 3, 21, 22, 23, 24 and 25 is respectively >40 (only grade 4), 58, 55, 58, >50, >50, 48 and 52. The average age in two studies from Japan[6] and Taiwan[26] was respectively 35.4 and 38.4 years. In the Taiwan study pilocytic astrocytomas and older patients were excluded. In my research the average age would not change if the 2 pilocytic astrocytomas had been excluded. In the Taiwan study the average age would have been lower if the pilocytic astrocytomas had been included. The Japanese study suggests that Japanese patients with astrocytomas grade 3 or 4 are younger than patients with the same disease in the Western world. These facts also suggest that younger patients with an astrocytoma grade three or four are more likely to enter an "alternative" (orthomolecular) practice than older patients with one of these astrocytomas; at least in the West. What is far more interesting is survival. Median survival was 18 months and ten days. Excluding the two pylocytic astrocytomas, median survival was 13 months. **Table 4** shows survival for the whole group, the grade 4 subgroup and the grade 3 subgroup with and without the 2 pilocytic grade 3 astrocytomas.

It is remarkable that the patients in this pilot study have a significantly better survival than any group of similar patients already mentioned in references. This means that I only aim at a comparison with groups for which no preselection was made and in which no chemotherapy was applied. Secondary references confirm this picture. Look for example at the table in reference 6, page 489.

In the introduction it has been made clear that age is an important prognostic factor. However, not everyone thinks this way,[25] perhaps because people over 50 usually have a worse prognosis.[23] It is also true that grade 4 tumours are relatively more

Table 4. Long-term Survival of Patients by Grading.

group	1 year survival	2 years survival	3 years survival
total (N=17)	14 (82%)	6 (35%)	4 (24%)
grade 4 (N=10)	8 (80%)	1 (10%)	1 (10%)
grade 3 + pilocytic astrocytomas (N=7)	6 (86%)	5 (71%)	3 (43%)
grade 3 without pilocytic astrocytomas (N=7)	4 (80%)	4 (80%)	2 (40%)

frequent at older ages.[27] Therefore we decided to conduct a statistical comparison between our group and three (sub)groups from literature, having a lower average age than our group. We found three such groups. First Yonoyama *et al*[6] Chi-square testing[28] shows a significantly better one year survival (82% versus 52%); the group of Yonoyama *et al* consisted of 127 persons; survival is significantly better in our group($P<0.05$). Two and three year survivals are not significantly different. This result is solid, because people in the group of Yonoyama *et al* were on the average younger, more often operated upon, more often given radiation treatment and there were fewer brain stem astrocytomas in their group. The second group is Dutch,[25] consisting of 25 patients with ages between 17 and 39; 16 had grade 3 and 9 had grade 4. Of the grade 3 patients 8 had not been treated with radiation; their median survival was less than one month. The grade 3 patients given radiation treatment had a median survival of 17.5 months. The grade 4 patients, who had not been given radiation treatment (4 pts) had a median survival of less than one month; while those who (5 pts) had been given radiation treatment, had a median survival of 8.9 months. A higher average percentage of this group than in ours had been operated upon (respectively 89 and 47 per cent).

We now will compare our group only to the grade 3 and 4 patients who had been given radiation treatment. First we adjust the high level of grade 3 tumours in this group; on the basis of the median survivals it is easy to find that their total median survival would have been 12.5 months if the relative numbers of grade 3 and 4 in that group had been equal to ours. A chi-square test to establish the odds of being alive after 12.5 months shows that significantly more patients were alive in our group (11 in our group and 6.5 in the other; $P<0.05$).

The third group to be compared with, is a subgroup of North *et al*.[22] This is a subgroup of 39 patients, who were all younger than 40; 67% of them had been operated upon (versus 47% in our group) and 82% had been given radiation treatment, while this was 94% in our group. Biopsy and radiotherapy were also found to be slightly less effective than mere surgery (**Table 4,** page 56). After one year, 23 of the 39 patients of the group referred to were alive. This is (according to a chi-square test) significantly less than in our group ($P< 0.05$). So the main conclusion is that our group, in spite of having a poorer prognosis on the basis of partly interrelated risk factors, had a significantly better life expectancy. Taking the three groups together and comparing this with our group, expresses the difference even more significantly. Average survival after three years is only known for the groups of Yonoyama et al and North *et al*, and is slightly higher in the group of North et al and lower in the group of Yonoyama *et al*. Altogether three year survival is non-significantly better in our group.

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