COMMENTARY

Chemotherapy for Glioblastoma

Is Costly Better?

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An international study under the guidance of the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada caused a furor in 2005. Patients with glioblastoma who had received temozolomide (TMZ) during and after radiotherapy lived significantly longer than those who had received radiotherapy alone. The news was covered widely by the media as a breakthrough in brain tumor research. Today, the application of TMZ concomitantly with radiotherapy and thereafter is considered the new treatment standard for this aggressive brain tumor. A phase 3 trial performed by the Neuro-Oncology working Group of the German Cancer Society (NOA) that yielded better survival data than any prior phase 3 study for glioblastomas had been published 2 years before. Radiochemotherapy either with nimustine (ACNU) and teniposide or with ACNU plus cytarabine yielded median survival and 2-year survival rates at least equal to those of the EORTC trial. The drugs cost much less than TMZ. However, although the study results were published in a high-ranking medical journal as well, they received much less publicity, and none of the NOA protocols has become generally accepted. After comparing the 2 studies in detail, as well, the author of this report suggests conducting a new phase 3 trial comparing the 2 regimens to determine whether TMZ is justified further as standard for the treatment of glioblastoma.

In 2003, the Neuro-Oncology Working Group of the German Cancer Society (NOA) published a randomized study (NOA-1) in patients with malignant glioma.[1] It compared 2 radiochemotherapy combinations of nimustine (ACNU) with either teniposide (VM26) or cytosine arabinoside (ara-C). The median survival and the 2-year survival rates for both arms were approximately equal but exceeded those from all prior phase 3 studies. Nevertheless, the results from that study have remained widely unnoticed.

Two years later, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) published a study in which temozolomide (TMZ) during and after irradiation was compared with radiotherapy only.[2] The outcome of the treatment arm was similar to the outcome reported in the NOA-1 trial. In contrast to the German study, this

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Received June 2, 2008; accepted June 23, 2008.

DOI 10.1002/cncr.23884
Published online 2 October 2008 in Wiley InterScience (www.interscience.wiley.com).

result was communicated widely in the scientific and lay press. In the meantime, the TMZ regimen has become the new standard for glioblastoma (GB) treatment.

It can only be speculated why NOA-1 was ignored. Maybe the large number of previously unsuccessful studies with other chloroethylnitrosoureas (CENUs) played a role. Or perhaps it was the radiotherapy-only arm of the EORTC study, which demonstrated the TMZ effect more convincingly. The NOA-1 trial did not include one, because, when the trial was initiated in Germany, it was no longer considered ethically justifiable to have a radiotherapy-only arm for malignant gliomas.[1] The objective of this commentary was to recall these important results, especially because the NOA-1 treatment regimen appears to be very cost effective.

RESULTS

NOA-1 Study

The NOA-1 trial compared 2 radiochemotherapy arms. In total, 362 patients with GB or anaplastic astrocytoma (AA) received radiotherapy and up to 5 cycles of either ACNU plus VM26 or ACNU plus ara-C combination chemotherapy.[1] Both treatment alternatives were proven equally effective. With a median survival of 16 to 17 months, the GB patients lived considerably longer than after other forms of chemotherapy. Also, the 2-year survival rates (25% and 29%) exceeded those of all prior phase 3 studies (Table 1).

EORTC Study 26981

In total, 573 patients with glioma were recruited at 85 European and North American centers. All patients received radiotherapy, and 50% received TMZ during and after the irradiation phase (Table 1). The median survival of this group was 2.5 months longer (14.6 months vs 12.1 months) and their 2-year survival rate was higher by a factor of 2.5 (26.5% vs 10.4%) compared with the control group that received radiotherapy only.

Table 2 lists survival data from the NOA-1 and EORTC 26981 trials arranged according to various single variables (performance index, age, extent of surgery), as well as to Radiation Therapy Oncology Group (RTOG) risk groups (data from previous reports[1-3]). The drug costs for a typical treatment period, consisting of 5 or 6 cycles of the 3 different schemes, are provided in Table 3.

DISCUSSION

Careful reading of the original EORTC publication[2] reveals a weakness that has remained unnoticed even in a subsequent report by the study group.[3] The title and abstract in the original article refer to patients with newly diagnosed GB only. However, only 85% of the tumors were reviewed centrally; and, among these, 3% were diagnosed as AA, 3% were diagnosed as other histologies, and 1% were deemed 'inconclusive material.'

Patients who have other tumor entities must not be combined with the GB group, because they have another, often better prognosis.[4-6] The NOA-1 data in Table 1 illustrate that patients with AA patients, on average, live 3 to 4 times longer than patients with GB. Hence, every patient with AA who is erroneously assigned to the GB group increases the probability that the calculated survival is falsely extended.

If the AA patients in treatment arm I (ACNU plus VM26) or treatment arm II (ACNU plus ara-C) are grouped together with the GB patients, then the median survival increases by nearly 2 months, and the 2-year survival increases by up to 12 percentage points to an impressive 37%. In the EORTC study, the bias should not be as dramatic. Nevertheless, even a fraction of only 3% of AA patients can increase the median survival by a couple of weeks and the 2-year survival rate by 1 or 2 percentage points.[7]

Table 2 lists survival data from the NOA-1 and EORTC 26981 trials arranged according to various subgroups. The results sorted by performance index, age, and extent of surgery are influenced by the fraction of AA patients. This translates into a possibly overstated benefit for the NOA-1 treatment arms.

However, the situation is different for the RTOG risk groups, which classify patient populations with malignant glioma according to multiple prognostic variables, including histology. This yields refined patient subsets that are particularly suited for a direct comparison of different treatment regimens.[4,5] From Table 2, it is obvious that the NOA-1 trial was more favorable than the EORTC 26981 trial when the results are arranged according to these stratification criteria.

New treatment protocols are assessed not only for prolongation of life. Equally important is whether the protocols are tolerated well by the patients and that they have acceptable side effects. The combination of ACNU and ara-C was associated with significantly more toxicity than ACNU and VM26, and the latter combination caused leukopenia slightly more often than the TMZ regimen (Table 1). However, NOA-1 was designed for dose escalation where possible and deliberately accepted more side effects. In fact, 40% of patients in the ACNU plus VM26 arm

TABLE 1
Overview of Study Conditions and Results

Study	Patient Data	Treatment Scheme	Toxicity ≥ Grade 3/4 and Toxicity-Related Discontinuation	Median Overall Survival, mo			2-Year Survival Rate, %		
				GB	GB and AA	AA	GB	GB and AA	AA
EORTC 26981 (Stupp 2005[2])									
Entire cohort	AGE: Median 56 y (range 19–71 y); WHO PI, 0–2* EXTENT OF SURGERY: 16% biopsy only; 44% partial; 40% complete; SECOND SURGERY: 23%	RT (focused; 60 Gy in 2-Gy fractions in ≤6 wk with 3D-planning) ± ChT	14% leukopenia; 12% thrombopenia; 1% anemia; 7% infection; 13% discontinuation; 2 lethal hemorrhages						
Arm I (n = 287)	Pathological review: 221GB patients; 7 AA patients; 11 "other" patients	TMZ 75 mg/m^2 on d1–d40 (≤d49) every 4 wk; Cycle 2: 150 mg/m^2 on d1–d5; Cycles 3–6: 200 mg/m^2 on d1–d5	2% infection; <1% discontinuation		14.6			26.5	
Arm II (n = 286)	Pathological review: 229 GB patients; 9 AA patients; 8 "other" patients	RT only			12.1			10.4	
NOA-1 (Weller 2003[1])									
	AGE: Median 50 y (range 17–73) y [GB only, 55 y] KARNOFSKY PI ≥ 70* EXTENT OF SURGERY: 7% biopsy only; 32% partial; 40% complete; 21% no data; SECOND SURGERY: 16%	RT (focused; 60 Gy in 1.8–2 Gy fractions) w/ChT I or II							
Arm I (n = 183)	154 GB patients; 29 AA patients	ACNU 90 mg/m^2 on d1 plus VM26 60 mg/m^2 on d1–d3 every 6 wk, Cycles 2–5 (partly with dose escalation: ACNU 100 mg/m^2 and VM26 up to 20%)	20% leukopenia; 13% thrombopenia; 2% anemia; 11% discontinuation; 3 lethal infections	17.3	19.1	60	25	37	88
Arm II (n = 179)	147 GB patients; 32 AA patients	ACNU 90 mg/m^2 on d1 plus AraC 120 mg/m^2 on d1–d3 every 6 wk, Cycles 2–5 (partly with dose escalation: ACNU: 100 mg/m^2 and araC up to 20%)	58% leukopenia; 53% thrombopenia; 6% anemia; 13% discontinuation; 1 lethal infection	15.7	17.6	62.5	29	37	72

GB indicates glioblastoma multiforme; AA, anaplastic astrocytoma; EORTC, European Organization for Research and Treatment of Cancer; WHO, World Health Orgainization; PI, performance index; RT, radiotherapy; ChT, chemotherapy; Gy, grays; 3D, 3-dimensional; TMZ, temozolomide; NOA, German Cancer Society Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; araC, cytosine arabinoside.
*A WHO PI of 0–2 is comparable to a Karnofsky PI of 60–100.

TABLE 2
Comparison of Survival Data for Various Subgroups From German Cancer Society Neuro-Oncology Working Group Study NOA-1 Study and European Organization for Research and Treatment of Cancer Trial 26981

	Median Overall Survival, Mo			2-Year Survival Rate, %		
	NOA-1	EORTC 26981		NOA-1	EORTC 26981	
Variable	ACNU+VM26/ACNU+AraC	RT+TMZ	RT	ACNU+VM26/ACNU+AraC	RT+TMZ	RT
Performance index (WHO 0 or Karnofsky 100)	22.2	17.4	13.3	47/40	ND	ND
Age, y						
<50	24	17.4	13.2	56/47	ND	ND
≥50	15.8	13.6	11.9	21/29	ND	ND
Surgery	18.6	15.8	12.9	37	ND	ND
Biopsy only	9.9	9.4	7.9	19	ND	ND
RTOG risk groups*						
III	24†	21†‡	15	51†	43†‡	20
IV	16†	16†‡	13	23†	28†‡	11
V	15†	10‡	9	20†	17†‡	6

NOA-1 indicates the German Cancer Society Neuro-Oncology Working Group Study; EORTC, European Organization for Research and Treatment of Cancer; ACNU, nimustine; VM26, teniposide; AraC, cytosine arabinoside; RT, radiotherapy; TMZ, temozolomide; ND, no data available; WHO, World Health Organization; RTOG, Radiation Therapy Oncology Group.

*Patient classification according to Scott 1998.[5]

†Data significantly better than references from the RTOG data base.

‡Data from Mirimanoff 2006.[3]

TABLE 3
Drug Costs for Therapy According to the German Cancer Society Neuro-Oncology Working Group Study NOA-1 Scheme (Columns 4 and 5) or the European Organization for Research and Treatment of Cancer Trial 26981 Scheme (Column 6)*

				NOA-1		EORTC 26981
Variable	AraC	ACNU	VM26	AraC+ACNU	VN26+ACNU	TMZ
Cost, Euro†						
5 mg	ND	ND	ND			8
20 mg	ND	ND	ND			29
50 mg	ND	57	19			ND
100 mg	7	ND	ND			132
250 mg	ND	ND	ND			238
Cycle 1						
Dose/d, mg/m^2	120	90	60			75
Dose/d, mg/1.86 m^2	223.2	167.4	111.6			139.5
Cost/d, Euro	21	228	57			190
Treatment d/cycle	3	1	3			40
Drug cost/Cycle 1	63	228	171	291	399	7600
Cycle 2						
Dose/d, mg/m^2	120	90	60			150
Dose/d, mg/1.86 m^2	223,2	167.4	111.6			279
Cost/d, Euro	21	228	57			283
Treatment d/cycle	3	1	3			5
Drug cost/cycle 2	63	228	171	291	399	1415
Cycle 3-n						
Dose/d, mg/m^2	120	90	60			200
Dose/d, mg/1.86 m^2	223.2	167.4	111.6			372
Cost/d, Euro	21	228	57			399
Treatment d/cycle	3	1	3			5
No. of cycles	3	3	3	3	3	4
Drug cost/Cycle 3-n	189	684	513	873	1197	7980
Total drug cost, Euro	315	1140	855	1455	1995	16,995

NOA-1 indicates the German Cancer Society Neuro-Oncology Working Group Study; EORTC, European Organization for Research and Treatment of Cancer; AraC, cytosine arabinoside; ACNU, nimustine; VM26, teniposide; TMZ, temozolomide; ND, no data available.

*The data refer to the acquisition costs only and were calculated for a patient with 1.86 m^2 body surface area.

†The prices per unit are taken from published price lists (2007).

had their ACNU doses escalated, but only 6% needed reductions. The side effects did not cause more treatment discontinuations among patients in the NOA-1 trial (Table 1). With 11% and 13%, respectively, they were in the same range as in the EORTC trial (13%). Finally, Table 1 also illustrates that the number of uncontrollable serious incidents was similar for the 3 chemotherapy arms.

At first sight, the competitive outcome of the NOA study may be surprising, given the many less favorable survival data from other, earlier CENU trials. However, contrary to what often has been depicted, CENUs have demonstrated different effectiveness and selectivity in vitro and in vivo.

For example, ACNU is less toxic to the lung than carmustine.[8] This is the major reason why ACNU is preferred in Japan and in some European countries. In vitro experiments tend to explain this difference by illustrating the different selectivity of the various CENUs toward O6-methylguanine-DNA methyltransferase (MGMT)-expressing cells. ACNU is considered more discriminating than carmustine and lomustine (CCNU). Mucous producing Clara cells, which supposedly are very low in MGMT activity,[9] are spared better by ACNU than by the other agents.

Among solid tumors, brain tumors also are considered low-expressing MGMT tumors. Therefore, it was predicted that ACNU would be more effective than other CENUs in conveying a therapeutic response with less nonspecific toxicity.[10] This prediction was confirmed in a recent report. A survival gain analysis of 24,000 patients with high-grade glioma who were treated with various CENUs demonstrated the greatest gain in survival for ACNU-treated patients (+8.9 months). CCNU yielded a survival gain of +5.9 months, and, for carmustine—the most widely used CENU—no gain was discernable.[11]

Effectiveness and toxicity, at least for ACNU and VM26, seem comparable to those for TMZ. However, the differences in cost between the study medications are tremendous.

During the first cycle of the EORTC protocol, TMZ has to be administered daily. This causes drug costs of approximately 7600 Euros (Table 3). In the adjuvant phase, the drug needs to be taken for 5 days per cycle only, although at higher doses. This results in costs ranging from 1400 to 2000 Euros per additional cycle. The same patient treated with 1 of the NOA-1 schemes would require cytostatic drugs for costs of only 300 or 400 Euros per cycle.

The cost for the whole treatment period amounts to approximately 17,000 Euros for TMZ, roughly 2000 Euros for ACNU plus VM26, and only 1500 Euros for ACNU plus ara-C. Even considering the additional charges to administer VM26 or ara-C as infusions ($\leq$100 Euros per application), the cost for TMZ remains a multiple of the cost of the other drugs. Severe emesis was rare in the NOA study (grade 3 or 4 events on $<$1.5% of study days) and did not result in significant extra cost.

Wasserfallen et al[12] calculated similar values for the drug cost. They estimated that the total cost of care for the treatment of a GB patient with TMZ was approximately 34,000 Euros with 55% of that cost attributable to the acquisition of the drug.

Considering the cost-effectiveness data, it is surprising that none of the NOA-1 protocols has found wider acceptance. Even more surprising, the 2 cytotoxic drugs VM26 and ara-C currently are not approved for the treatment of glioma in Germany. Application of ara-C was authorized only for the NOA-1 study. The manufacturer of VM26, conversely, did not ask for extension of approval of the product in 2006; rather, it was withdrawn completely from the German market. VM26 still can be imported from other European countries. However, it can be administered only to GB patients within an individual treatment decision but not as a general recommendation.

Whenever differences in survival and objective side effects are small, large discrepancies in cost can be justified only by a significant improvement in subjective quality-of-life (QoL) parameters. Internationally accepted upper benchmarks for the cost per quality-adjusted life year are in the range from 40,000 to 45,000 Euros.[13] The incremental cost of TMZ per quality-adjusted life year may be above this upper limit.[12,14]

The enormous costs of TMZ with hitherto undiscernable advantages compared with ACNU plus VM26 suggest the need to start a direct comparison of the 2 regimens in a new prospective, randomized, phase 3 trial in patients with GB. According to Wolff et al,[11] it may be sufficient to compare TMZ with ACNU only. Their survival gain analysis for various nitrosoureas with or without additional drugs revealed the highest survival gain for ACNU-based treatments compared with 6 other nitrosoureas. In addition, ACNU combination protocols did not result in significantly higher effectiveness than treatment with ACNU alone. Therefore, a direct comparison of TMZ and ACNU may be worth consideration. The finding that both drugs can be administered orally is another asset of such an approach.

In contrast to the EORTC study, patients in the NOA study were not stratified for MGMT methylation.[15] However, the MGMT enzyme removes TMZ residues as well as chloroethyl residues from O6-guanine in DNA. A recent Japanese study[16] correlated the expression of MGMT measured immunohisto-

chemically and the survival of patients with GB after ACNU-based chemotherapy. Among only 18 patients with GB, a trend was observed toward longer progression-free survival for patients who had low MGMT-expressing tumors (15 months vs 9 months; $P = .09$), and a statistically significant difference was observed in overall survival (22 months vs 12 months; $P = .01$). A second Japanese group that studied hypermethylation of the MGMT promoter observed extended survival only for patients with AA, but not for patients with GB, after ACNU treatment.[17] Although the results were discrepant, these first data indicate that it also may be worthwhile to consider MGMT status for CENU-based chemotherapy. It is noteworthy that hypermethylated MGMT gene status did not appear to provide an additional benefit in the recursive partitioning analysis (RPA) of the EORTC patients in any of the RPA classes.[3] A direct comparison between TMZ and ACNU (with or without VM26) in this respect also would be interesting. Finally, such a study should include full assessment of QoL and overall cost. This would make it possible to investigate whether the more expensive treatment variant would be warranted because of better QoL.

In conclusion, the treatment results from the NOA-1 and EORTC 26981 trials appear to indicate that ACNU plus VM26 (or ara-C) can be as effective as TMZ for patients with GB but is much less costly. Therefore, we suggest starting a direct comparison of these successful regimens in a new prospective, randomized, phase 3 trial. Such a study should include full assessment of QoL and overall costs to determine whether the disproportionately higher drug costs for TMZ are compensated by other costs or are justified because of better QoL.

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