Anti-Cancer Drugs 1998, 9, pp. 515 524

Research paper

Evaluation of ocular safety: tirapazamine plus cisplatin in patients with metastatic melanomas

Thomas C Prager, Judianne Kellaway, Yali Zou, Richard G Urso, Susan McIntyre[1] and Agop Y Bedikian[1]

Department of Ophthalmology and Visual Science, University of Texas Health Science Center, Houston, TX 77030, USA. [1]Department of Medicine, Melanoma and Sarcoma, MD Anderson Cancer Center, University of Texas, Houston, TX 77030, USA.

Ninety-six patients with metastatic melanoma treated with two consecutive tirapazamine–cisplatin combination chemotherapy regimens were followed for signs of therapy-related ocular toxicity. Baseline and follow-up data were obtained such that each patient acted as his own control. A battery of vision-related tests was performed. These included: best corrected visual acuity, color vision, retinal fundus examination and electro-oculograms (EOG). A brief health-related quality of vision test was administered at each follow-up visit to detect and evaluate self-perceived changes in visual status. In the first study, 48 patients received i.v. tirapazamine over 2 h at 260 mg/m^2 (group 1) while in the second study 48 patients (group 2) received i.v. tirapazamine at 390 mg/m^2. Visual system assessment was conducted at three timepoints: first at baseline, then at 6 weeks post-baseline, i.e. after two courses of chemotherapy and visit two upon discontinuation of therapy. There was no difference in visual acuity between group 1 and group 2 at baseline, follow-up 1 or at follow-up 2. Grouped data indicate that visual acuity was not affected by either dosage of chemotherapy. Group 1 at baseline found 15% below the normal EOG cutoff point, increasing to 23% at follow-up 1 and increasing at follow-up visit 2 to 33%. Group 2 demonstrated the same EOG findings, but the results were more magnified: baseline, 24%; follow-up 1, 44%; and follow-up 2, 44%. After eliminating those with abnormal color vision baselines, 21% (nine of 42) group 1 patients demonstrated abnormal color vision total error scores at follow-up 1 and 16.7% (four of 24) at follow-up 2. Few individuals showed changes in the higher dosage group. With the exception of one person in each dosage group, all changes were along the blue–yellow (tritan) axis, which is associated with acquired color defects. Of 96 patients examined, proven fundus changes were found in only four subjects. These fundus findings included retinal hemorrhages, retinal nerve fiber layer infarcts (cotton wool spots) and small retinal pigment epithelium detachments. There was no systematic statistical significant difference among the various measures of visual system outcome between groups or test times. Data from all tests for individual patients in both groups reveals a sporadic distribution of changes in visual system tests. If toxicity were pronounced, one would expect consistency in the findings and all or most of the assessment tests would be abnormal for a particular patient. However, patients who were abnormal on one measure of acuity were not necessarily abnormal on the other measures. []

Key words: Cisplatin, metastatic melanoma, ocular toxicity, tirapazamine.

Introduction

Ninety-six patients with metastatic melanoma treated with two consecutive tirapazamine-cisplatin combination chemotherapy regimens were followed for signs of therapy-related ocular toxicity. These patients were treated with cisplatin combined with a new bioreductive anti-cancer agent, benzotriazine di-*N*-tirapazamine.[1] It selectively targets tumor cells due to preferential toxicity for hypoxic cells frequently associated with solid tumors and not present in normal tissues.[1,2] Melanomas typically remain resistant to cancer therapies including irradiation and anti-cancer drugs. Repeated treatments with a combination of bioreductive drugs and chemotherapy cause lethal damage to the hypoxic tumor cells while sparing the bordering normal tissues.[3] Preclinical studies show that synergistic antitumor activity results from a schedule-dependent interaction between tirapazamine and cytotoxic drugs such as cisplatin.[4]

Previous human and animal chemotherapy trials have reported therapy-related ocular toxicity. High-dosage cisplatin was associated in one study with cortical blindness and retinal toxicity in eight of 13

Supported by Sanofi-Winthrop Pharmaceutical Research Division, Malvern, PA, Research to Prevent Blindness, Inc., New York, NY, The Hermann Eye Fund and NEI core grant EY 10608.

Correspondence to TC Prager, Hermann Eye Center, 6411 Fannin Street, 7th floor, Houston, TX 77030 USA. Tel: (+1) 713 500-5997; Fax: (+1) 713 500-0673

patients (62%).[5] Intra-carotid administration of BCNU (carmustine), cisplatin or BCNU-cisplatin combination for recurrent malignant primary brain tumors has resulted in ipsilateral visual loss in eight of 11 (73%) patients.[6,7] Nine patients with advanced breast cancer were examined for visual complications after high-dose chemotherapy with cisplatin, cyclophosphamide and carmustine, and autologous bone marrow transplantation without total body irradiation or local head irradiation. Optic neuropathy and retinopathy developed in five (56%) patients.[8] With tirapazamine in the uveal tract, ocular changes were detected in dogs (photoreceptor degeneration) and rats (retinal exudates) during the conduct of some of the preclinical studies suggesting the potential for retinal toxicity (Sanofi, internal reports).

In this study we sought to follow a cohort of melanoma patients receiving tirapazamine-cisplatin combination chemotherapy to determine the incidence, nature and clinical relevance of ocular toxicity, if any, associated with this therapy. A battery of vision-related tests was performed. These included: best corrected visual acuity, color vision, slit-lamp examination of the anterior segment, retinal fundus examination and electro-oculograms (EOG). The EOG, a non-invasive electrodiagnostic test, is reputed to be an indirect indicator of the health of the retina and retinal pigment epithelium, a site affected by ocular toxicity.[9-13] However, this light-induced response requires photoreception and therefore is not composed of purely retinal pigment epithelium signals.[14] The EOG has been reported to be abnormal in 66% of 59 patients with progressive cone or cone-rod dystrophies.[15] For reasons explained later, a more direct test of retinal function, the electroretinogram (ERG), was considered, but not used. Lastly, a brief health-related quality of vision test was administered at each follow-up visit to detect and evaluate self-perceived changes in visual status to help establish whether there is a correlation with the more objective and traditional ophthalmic findings.

Materials and methods

Patient population

A total of 96 patients with metastatic melanoma (stage IV) were enrolled in two consecutive tirapazamine-cisplatin combination phase II trials between November 1994 and June 1997. This study was approved by the University of Texas Committee for the Protection of Human Subjects. The average age was 55 (SD=13 years) with a median age of 56. Males comprised the majority (73%) of the patient population. In the two studies reported here, baseline and follow-up data were obtained such that each patient acted as his own control. In the first study, 48 patients received i.v. tirapazamine over 2 h at 260 mg/m^2 (group 1) while in the second study 48 patients received i.v. tirapazamine at 390 mg/m^2. The dose of cisplatin in both studies was 75 mg/m^2, given i.v. over 1 h, starting 1 h from completion of the tirapazamine dose. Group 1 included nine patients (nine of 48=19%) with ocular melanoma mostly treated with enucleation of the affected eye and 16 (33%) patients with prior chemotherapy (13 including cisplatin). Group 2 included only those patients with metastatic cutaneous melanoma without prior chemotherapy. Patients with brain metastases were treated in both studies only if they were controlled with prior radiotherapy or surgery and the patients had good performance status. Patients were treated with tirapazamine-cisplatin combination every 3 weeks up to a maximum of eight courses. They were taken off study early if tumor progression was observed or after four courses when no objective tumor regression was observed. Moreover, treatment was discontinued following one of four outcomes: (i) any time after the first course of therapy when tumor progression is established, (ii) at 12 weeks if the tumor failed to regress or (iii) at approximately 24 weeks, upon completion of planned chemotherapy, or (iv) treatment-related toxicity other than ocular.

Visual system assessment was conducted at three timepoints: first at baseline, then at 6 weeks post baseline, i.e. after two courses of chemotherapy, and visit 2 upon discontinuation of therapy. While the interval to follow-up visit 1 was usually 6 weeks after baseline, the length of time to follow-up visit 2 varied depending on the duration of chemotherapy. On average, visual testing took place at baseline, 43 days later and finally 124 days (range 82-164) after baseline. Note that at the time of follow-up visit 1 or 2, patients had not been receiving chemotherapy for about 3 weeks. There was no significant difference in the age or sex distribution between the two groups as determined by one-way ANOVA.

Ophthalmic evaluation

Visual acuity was determined by a Bailey-Lovie eye chart. This test has several distinct advantages over the traditional Snellen test. The Bailey-Lovie chart overcomes limitations of the Snellen chart,[16,17] which include: unequal increments between lines of vision, unequal number of letters per line and varying

perceptual difficulty of individual letters per line. After viewing under standardized light conditions with best corrected vision (i.e. glasses or contacts in place, if required), the total number of letters correctly identified was converted by tabled values[18,19] to their Snellen equivalent and entered as datum.

Color vision was evaluated by the Lanthony Desaturated Hue Test where 15 caps of pastel colors, viewed under standardized lighting (greater than 1000 lux) are arranged sequentially from blue to red (Munsell value 8 and chroma 2). A computer program provided by Vingrys and King-Smith[20] quantitatively scores the color vision panel test using Bowman's quantitative estimate of total color difference score.[21] Total error scores above 17.5 are considered abnormal. The axis of color confusion (protan, deutan or tritan) was determined by confusion angle computed by the method of Vingrys and King-Smith[20] and by visual inspection. Color deficiency angle scores are protan =3 to +17, deutan −4 to −11 and tritan greater than −70. We note that *most* acquired color defects, such as a consequence of toxicity, fall along the blue-yellow (tritan) axis.

Following the determination of visual acuity and color vision the patient was dilated and the anterior segment (lids, tear film, conjunctiva, cornea, iris, lens and anterior vitreous) was carefully screened by a staff ophthalmologist. The retina of each patient was evaluated and a drawing of the retina entered into the chart which was further documented by wide angle fundus photography. The color photographs of all patients at all visits were later evaluated by one of the authors (JK), a retinal specialist, who noted any changes and the type and extent of retinal change by inspecting the fundus photos under high magnification. Since any vascular changes were rare, fluorescein angiography was not put in this protocol. The vast majority of patients would have shown normal results with this time consuming and expensive test. It would not have added useful information since fluorescein angiography usually only confirms what one is observing clinically.

The EOG was conducted in dark (scotopic) and light (photopic) conditions after each patient was baseline stimulated with 5 min of standardized light. We followed the standard[22] established by the International Society for Clinical Electrophysiology of Vision. A Nicolet C-4 electrophysiology unit and ganzfeld stimulator bowl were used to gather EOG data. Patients were tested in the dark for approximately 20 min and then under standardized light conditions for an equal amount of time. The amplitude of the light peak (in μV) was divided by the dark trough to produce the so-called Arden ratio. The literature states that values above 1.7 or 1.85 indicate normally functioning retinal pigment epithelium. To determine normal variability five adult subjects received test-retest evaluations. Average (and median) baseline Arden ratio values were: right eyes=1.88 (1.74), left eyes=1.99 (2.02). Retest ratios were right eyes=2.00 (1.95), left eyes=2.01 (1.95). The average for right and left eyes over five subjects was 1.94 on test and 2.00 on retest or a 3% difference. Using median values, variability equals 3.7%. Since these normal test subjects were young, healthy and motivated, variability might be lower than in the general population and certainly lower than our cohort of sick patients. Since test-retest variability has been reported to be 17%,[23,24] to be conservative 25% will be taken as an abnormal test-retest score.

Visual quality of life questionnaire

We attempted to assess the patient's perception of visual changes during their course of chemotherapy by asking specifically about overall quality of vision, visual acuity, color vision and night vision. At the top of each questionnaire form was the following statement: 'We are interested if your course of chemotherapy has had a noticeable affect on your vision. Please indicate your answer to each question based on your best vision with glasses or contact lenses. Your answers should reflect your general capabilities over the past month'. Patients were tested at first follow-up and then after completion of chemotherapy. For each question (e.g. 'To what extent has your visual acuity—ability to see detail—been affected?') the patients responded: (0) not at all, (1) slightly, (2) somewhat, (3) moderately and (4) severely. While each question was analyzed individually, the total for each patient was divided by the highest possible sum of all questions (maximum possible =16) to give a percent estimate of visual impairment. For example, if the patient's total score is 4 (color vision affected moderately and visual acuity affected slightly) divided by the total possible (16) yields a visual decrement estimate of 25%. A paired *t*-test and one-way ANOVA was performed on first and second visit follow-up data to determine a change in perceived visual impairment between chemotherapy and off-study perceptions and between group differences.

Results

Of the 48 subjects in group 1 (dosage=260 mg/m^2 tirapazamine and 75 mg/m^2 cisplatin) 47 returned for first follow-up. For 23 of the 47 patients the first follow-up testing became the off-study test session because they were taken off therapy due to tumor progression. One patient was too sick to have follow-

up testing and was taken off chemotherapy. Twenty-three out of 27 who continued chemotherapy had subsequent study evaluation while the remaining four patients were too sick to participate. Of the 48 group 2 patients (dosage=390 mg/m^2 tirapazamine and 75 mg/m^2 cisplatin), 43 had follow-up evaluation after two courses of chemotherapy, and five were too sick to have visual testing and were taken off chemotherapy. Twenty-three of 43 patients had tumor progression and were taken off study. Of the 20 patients who

Table 1. Summary of change in vision-related measures at follow-up (FU) 1 and 2: comparison between chemotherapy dosage groups

Group	Subject no.	Sex	Age (years)	FU 1 (days)	FU 2 (days)	Visual acuity change		Color vision change		EOG change		Fundus change	Quality of vision	
						FU 1	FU 2	FU 1	FU2	FU 1	FU 2		FU 1	FU 2
1	1	F	49	40		yes		no		no		no		
1	2	M	46	44		yes		no		no		no		
1	3	M	31	42		no		no		no		no		
1	4	M	62	41	132	no	no	no	no	no	yes	no		
1	5	F	70	41	126	yes	no	no	no	no	yes	yes		
1	6	F	64	41	83	no	no	no	no	no	no	no		
1	7	M	32	32		yes		no		yes		no		
1	8	M	48	37		no		no		no		no		
1	9	M	71	47		no		no		yes		no		
1	10	M	54	40		no		no		no		no		
1	11	M	75	41	83	no	no	no	no	no	no	yes		
1	12	M	58	43	77	no	no	no	no	no	no	no		
1	13	M	56	43		yes		no		no		no		
1	14	M	56	39		no		yes		no		no		
1	15	F	71	45	91	no	no	no	no	yes	yes	no		
1	16	M	47	48	92	no	no	no	no	no	no	no		
1	17	F	57	40	189	no	no	yes	yes	no	yes	no		
1	18	F	70	45	212	yes	yes	yes	yes	yes	yes	no		
1	19	M	55	43	70	yes	yes	no	no	no	no	no		
1	20	M	67	62		no		no		no		no		
1	21	F	50	41		no		no		no		no		
1	22	M	67	41		no		no		yes		no		
1	23	M	67	40	92	no	yes	no	yes	no	no	no		yes
1	24	M	60	42	97	no	no	no	no	no	no	no		yes
1	25	F	39	41		no		yes		yes		no		
1	26	M	64	22		no		yes		no		no		
1	27	F	49	42	237	no	no	no	yes	no	no	no		yes
1	28	M	35	44	156	no	no	no	no	no	yes	no	no	yes
1	29	M	59	42	85	no	no	no	no	no	yes	no	no	no
1	30	M	59	49		yes		yes		yes		no	yes	
1	31	F	68	48	210	no	yes	no	no	no	no	no	yes	no
1	32	M	52	36		yes		yes		no		no	yes	
1	33	F	63	42		no		no		yes		no	no	
1	34	M	71	43		no		no		no		no		
1	36	F	75	42	128	no	no	no	no	no	no	no	no	no
1	37	M	63	42	85	no	no	no	no	no	no	no		no
1	38	F	69	42	87	no	yes	no	no	no	no	no	no	yes
1	39	M	53	57		no		no		no		no	no	
1	40	M	41	43	86	no	no	no	no	no	no	no	no	no
1	41	M	59	43		no		no		no		no	no	
1	42	M	64	42	104	no	no	no	no	no	no	no	no	no
1	43	M	65									no		no
1	44	M	55	33		yes		yes		no		no	yes	
1	45	M	51	40	97	no	no	yes	no	yes	yes	no	yes	yes
1	46	M	69	42		no		no		yes		no	no	
1	47	M	72	39	85	no	no	no	no	no	no	no	yes	
1	48	M	22	44	177	no	no	no	no	no	no	no	yes	

Continued

continued chemotherapy, 16 had subsequent off-study evaluation, two are still taking chemotherapy and two were too sick to have the testing.

Table 1 is a complete compilation of all patient data in both groups. Criteria for a clinically significant change is explained in the following sections. Table I summarizes data from all patients, including basic demographic information, at follow-up 1 and follow-up 2, noting changes in visual acuity (greater than two lines), color vision (>17.5), EOG (<1.70), acquired

Table 1. Continued

Group	Subject no.	Sex	Age (years)	FU 1 (days)	FU 2 (days)	Visual acuity change		Color vision change		EOG change		Fundus change	Quality of vision	
						FU 1	FU 2	FU 1	FU2	FU 1	FU 2		FU 1	FU 2
2	49	M	63	43									no	
2	50	F	62	43	83	no		no		no	no	no	no	no
2	51	M	71	42	342	no		no		yes	yes	no	yes	
2	52	F	52	26		no		no		yes		no	yes	
2	53	M	72	41	175	no		no		no	yes		no	no
2	54	F	35									no		
2	55	M	44	41		no		no		yes		no	yes	
2	56	F	70	42	86	yes	yes	no	no	no	yes	no	no	no
2	57	M	52	41		no		yes		yes		no	yes	
2	58	F	42	30		no		no		no		yes	yes	
2	59	M	42	48		yes	no	no	no	yes	no	no	no	yes
2	60	F	54	48		no		no		yes		no	yes	
2	61	M	51	44		no	no	no	no	no	no	no	yes	yes
2	62	M	57	44		no		no		no		no	yes	
2	63	M	42	48	90	no	no	no	no	no	no	no	no	no
2	64	M	35	43		no		no		no		no	no	
2	65	F	67	50	163	no	no	no	no	yes	yes	no	yes	yes
2	66	M	56											
2	67	M	70											
2	68	M	69	42		yes		no		no		no		yes
2	69	F	51	21	43	no	no	no	no	yes	yes	no	yes	yes
2	70	M	42	24		no		no		no		no	yes	
2	71	M	65	42	146	no	yes	no	no	no	yes	no	yes	
2	72	M	40	50		no		yes		no		no	yes	
2	73	F	64	42		no		no		yes		no	yes	
2	74	M	59	43		no		no		yes		no	yes	
2	75	F	45	49	205	no	no	no	no	no	yes	no	no	
2	76	M	34	46		no		no		no		no	no	
2	77	M	51	41	133	no	no	no	no	no	no	no	yes	
2	78	M	40	64		no		no		no		no	no	
2	79	M	42	45		no		no		no		no	no	
2	80	M	39	47		no		no		yes		no	yes	
2	81	F	46	45	91	no	no	no	no	yes	n o	no	yes	
2	82	M	36	44	86	no	no	no	no	yes	yes	yes	no	
2	83	F	28	49		no		no		yes		n o		
2	84	M	51	47	77	no	no	no	no	no	no	no	no	yes
2	85	M	54	43		no		no		no		no	yes	
2	86	M	23	45		no		no		yes		no	no	
2	87	M	64	44	119	no	no	no	no	yes	no	no	no	yes
2	89	M	40											
2	90	M	63	30		no		no		no	no	no	no	
2	91	M	60	42		no		no		no		no	no	
2	92	M	73	49		no		no		yes		no	yes	
2	93	F	44	42		no		no		no		no	yes	
2	94	M	51	47		n o		no		yes		no	yes	
2	95	F	77											
2	96	M	68											
2	97	M	72											

fundus lesions and self-rated quality of vision (> 10%). Criteria for change in visual status for the various tests are further explained in the following sections.

Visual acuity

There was no difference in visual acuity between group 1 and group 2 at baseline, follow-up 1 or at follow-up 2. Means ± SD and ANOVA *F* and probability values are summarized in Table 2. Grouped data indicate that visual acuity was not affected by either dosage of chemotherapy, with mean and median values differing no more than one-half of a line of vision over time. Inspecting the results to identify outliers, at follow-up 1, nine group 1 patients (nine of 46=19.5%) lost two or more lines of vision, but three patients (three of 46=6.5%) apparently gained two or more lines of acuity over baseline values. In group 2, three patients (three of 42=7.1%) lost two or more lines of acuity and six gained vision (six of 46=13%).

At follow-up 2, when patients had completed their last course of chemotherapy, five of 23 group 1 patients (22%) lost acuity. One of these patients markedly lost vision with a reported change from a baseline value of 20/23 to 20/60. One patient gained two lines of vision. For group 2 patients two of 13 (15.4%) lost acuity. One patient demonstrated a change from 20/21 to 20/55. No patients gained acuity.

Table 2. Visual acuity at baseline, follow-up 1 and follow-up 2: comparison between chemotherapy dosage groups

	Geometric mean	SD	Median	*F* and *p* values
Baseline				
Group 1 (*n*=48)	20/21.90	14.75	20/20	*F*=0.62,
Group 2 (*n*=46)	20/22.13	28.9	20/20.47	*p*=0.43
Follow-up 1				
Group 1 (*n*=48)	20/22.62	19.94	20/20	*F*=1.47,
Group 2 (*n*=41)	20/21.73	7.29	20/20	*p*=0.23
Follow-up 2				
Group 1 (*n*=24)	20/23.26	12.21	20/20.94	*F*=0.14,
Group 2 (*n*=13)	20/22.85	9.22	20/20.94	*p*=0.71

EOG

The lower dosage group (1) had an average (SD) Arden ratio of 2.16 (0.46) at baseline with values greater than 1.70 considered normal. The Arden ratio fell slightly at follow-up 1, 2.07 (0.52) and slightly further when tested following cessation of chemotherapy [follow-up 2, 1.95 (0.36)]. Group 2 findings parallel these results, but Arden values were lower at each time point including baseline (see tabulated data in Table 3). The differences between

Table 3. EOG at baseline, follow-up 1 and follow-up 2: comparison between chemotherapy dosage groups

	Mean	SD	Median	ANOVA *F* and *p* values	Percent patients < 1.70	Percent patients worse than baseline	Percent patients better than baseline	Ratio of worse to better
Baseline								
Group 1 (*n*=89 eyes, 46 pts)	2.16	0.46	2.11		15% (7/46)	NA	NA	NA
				F=6.56, *p*=0.01		NA	NA	NA
Group 2 (*n*=96 eyes, 48 pts)	2.01	0.36	1.99		25% (12/48)	NA	NA	NA
Follow-up 1								
Group 1 (*n*=83 eyes, 44 pts)	2.07	0.52	1.98		23% (10/44)	25% (11/44)	9% (4/44)	1:2.56
				F=8.26, *p*=0.005				
Group 2 (*n*=82 eyes, 41 pts)	1.87	0.39	1.82		44% (18/41)	22% (9/41)	17% (7/41)	1:1.29
Follow-up 2								
Group 1 (*n*=43 eyes, 24 pts)	1.95	0.42	1.93		33% (8/24)	33% (8/24)	0% (0/24)	NA
				F=1.08, *p*=0.30				
Group 2 (*n*=32 eyes, 16 pts)	1.85	0.36	1.74		50% (8/16)	44% (7/16)	13% (2/16)	1:3.38

groups was significant at baseline (F=6.56, p=0.01), marked at follow-up 1 (F=8.26, p=0.005) and no difference at follow-up 2. The percentage of patients that were below the normal Arden ratio of 1.70 appears to increase for both groups over time, possibly suggesting a cumulative drug effect. Group 1 at baseline found 15% below the normal cut-off point, increasing to 23% at follow-up 1 and increasing at follow-up visit 2 to 33%. Group 2 demonstrated the same findings, but the results were more magnified: baseline, 24%; follow-up 1, 44%; and follow-up 2, 44%.

The percentage of patients whose Arden ratio changed from baseline by more than 25% was computed for each visit for both groups. There seems to be marked variability in the EOG findings since a substantial number of patients, also appear to have improved their Arden ratio at subsequent visits by 25%. Table 3 summarizes these results. To normalize these outcomes a ratio was formed from the percentage that had worse Arden ratios to those whose values were better. More patients appear to have a reduction in the Arden ratio than those who gain or improve: Group 1 at follow-up 1, 1:2.56; follow-up 2, NA; Group 2 at follow-up 1, 1.29 and follow-up 2, 3.38.

Color vision

At baseline 12.5% (six of 48) of group 1 patients were abnormal in contrast to 6% (three of 49) of the group 2 subjects. After eliminating those with abnormal baselines 21% (nine of 42) group 1 patients demonstrated abnormal color vision total error scores at follow-up 1, and 16.7% (four of 24) at follow-up 2. Few individuals showed changes in the higher dosage group. Only 4.5% (two of 42) were abnormal at follow-up 1 and 0% (none of 16) at the second follow-up visit. With the exception of one person in each dosage group, all changes were along the blue-yellow (tritan) axis, which is associated with acquired color defects.

Subjective quality of vision

Subjective quality of vision, as assessed by asking about four visual activities, was evaluated after the first and second follow-up with means, medians and SD detailed in Table 4. The sum of the responses divided by 16 (highest possible score) was used to derive the estimated percent visual decrement. While the follow-up 1 average decrement for group 1 (n=17) was 13.60% (SD 20.87%) the median value was only 6.25%. At follow-up 2 (n=13), off study, the visual complaints remained about the same, average 12.02 (SD 14.31%) median 0.00%. Large differences between the mean and median suggests the presence of outliers. A paired t-test on 13 subjects with data at both timepoints was not significant, t=0.19, p=0.85. Forty-seven percent reported an estimated visual decrement, greater than 10%, at follow-up 1 and unchanged at follow-up 2, 46%.

Group 2 patients reported higher values at both follow-ups: follow-up 1 (n=41, average 19.66% [12.60], median 12.50%); follow-up 2 (n=10, average 22.50% [22.48], median 18.75%). A paired t-test on nine subjects with data at both timepoints was not

Table 4. Subjective quality of vision at baseline, follow-up 1 and follow-up 2: comparison between chemotherapy dosage groups

		Follow-up overall	Visual acuity	Color vision	Night vision	Sum	Vision decline (%)
Follow-up 1							
Group 1	average	0.65	0.76	0.35	0.41	2.18	13.60
(n=21)	SD	0.93	1.03	0.86	0.80	3.34	20.87
						median	6.25
Group 2	average	1.00	1.05	0.44	0.66	3.15	19.66
(n=41)	SD	1.16	1.18	0.84	1.09	3.48	21.77
						median	12.50
Follow-up 2							
Group 1	average	0.77	0.92	0.15	0.08	1.92	12.02
(n=13)	SD	0.93	1.12	0.38	0.28	2.29	14.31
						median	0.00
Group 2	average	1.00	1.30	0.50	0.80	3.60	22.50
(n=10)	SD	1.05	1.34	0.85	0.92	3.60	22.48
						median	18.75

significant, $t=-1.34$, $p=0.21$. A one way ANOVA between groups at follow-up 1 was not significant, $F=0.95$, $p=0.33$ nor at the second follow-up, $F=1.86$, $p=0.19$. Compared to group 1 more group 2 patients reported visual decrement (greater than 10%) at follow-up 1 56% (versus 47%), than at follow-up 2, 60% (versus 46%).

Fundus findings

Following dilated fundus examinations by staff ophthalmologists, the notes on the funduscopic exams as well as photographs from all examinations were reviewed for a final determination by a retinal specialist (JK). Of 96 patients examined, proven fundus changes were found in four (4%, four of 96) of a total of 10 suspected patients identified by initial screening. These fundus findings included retinal hemorrhages, retinal nerve fiber layer infarcts (cotton wool spots) and small retinal pigment epithelium detachments. Baseline findings included retinal hemorrhages in two patients cotton wool spots in two patients and hypopigmented lesions or drusen were present initially in three patients. Since baseline retinal findings remained constant and did not change during the course of the study, these lesions therefore cannot be considered to be secondary to drug therapy.

However, four patients developed changes during the course of their involvement in this study. One patient (group 1) had a few cotton wool spots and small retinal hemorrhages in both eyes after treatment, and one patient (group 2) had an isolated small retinal hemorrhage in the right eye. Two patients (group 1) developed small (less that 50% disc area) retinal pigment epithelial detachments in the macula. The lesion had no effect upon one patient's vision and the other patient's visual acuity dropped by approximately one line. All of the clinical findings which occurred after the initiation of treatment are not considered to be of significant enough nor severe enough nature to cause discontinuation of the drug regimen. No patients exhibited clinical macular changes which would signify retinal toxicity, e.g. such as pigmentary changes, retinal deposits, retinal thinning, vascular changes or bull's eye maculopathy.

Anterior segment examinations did not reveal significant changes in any of the study patients.

Discussion

In this series of 96 patients with metastatic melanomas who received two dosage levels of tirapazamine plus cisplatin there was no systematic statistical significant difference in the various measures of visual system outcome between groups or test times. However, there was a trend toward slightly more visual problems in the higher dosage group on some of the tests. Inspection of Table 1, which summarizes data from all tests for individual patients in both groups, reveals a sporadic distribution of changes in visual system tests. If toxicity were pronounced, one would expect consistency in the findings and all or most of the assessment tests would be abnormal for a particular patient. However, patients who were abnormal on one measure of acuity were not necessarily abnormal on the other measures.

Any measure that requires a subjective response from the patient has the potential for bias and increased measurement variability, especially if the patient population is sick. If patients are faced with deteriorating health and are asked to focus on a particular aspect of functional impairment, it is difficult to be absolutely sure of the veracity of the responses. We note that the most objective measure, evaluation of fundus photography, demonstrated acquired change in only 4% (four of 96) of patients examined and three of the four were in the lower dosage group. No patient was found to have macular alterations nor were pigmentary changes detected nor did those who had baseline retinal damage have subsequent worsening.

Median visual acuity was in the 20/20 range at all time points for both groups. While some patients lost more than two lines of vision, others reported gaining acuity. When this test-retest variability is net-corrected (by subtracting gainers from losers), at follow-up visit 1,13% of the group 1 patients lost vision and 6% of the group 2 patients had a net gain. At follow-up visit 2, when patients had completed chemotherapy, 17% (four of 23) of group 1 subjects lost vision as did 15% (two of 13) of group 2 patients. Thus, there was more of a change in the group 2 patients between follow-up visit 1 and 2, but the sample size was small.

Color vision changes were more apparent in the low dosage group (21% follow-up 1 and 17% at follow-up 2) versus 5 and 0% in the high dose group, which goes against the expectation of more complications with higher dosage. However, we cannot exclude the possibility of this being a tirapazamine-associated toxicity. Color vision changes associated with toxicity, an acquired defect, show anomalies along the blue-yellow axis, which was the case in essentially all subjects tested.

We anticipated an increase in variability associated with the EOG when testing the sick and possibly uncooperative patient population. Based on our pilot

data in normals we thought we would encounter less variability than reported in the literature. Published intersubject variability appears to be 17% in normals,[23] which is consistent with a weighted coefficient of variation (SD/mean) of 17.37% in five studies, 600 patients, summarized by Alanki in 1984.[24] In another publication, intrasubject variability of 7% for the same eye and 14% between eyes was found in 16 subjects retested over three trials.[25] In normals, our single eye test-retest variability was only 3% and relative to baseline, group 1 varied 4% at the first follow-up 1 and 7% at follow-up 2; similarly group 2 patients were 7 and 8%, respectively. Averaging over groups and follow-up we found 28% of our patient population demonstrated a 25% decrease (worsening) in EOG ratio, but 10% showed an increase (improvement).

When considering those with abnormal EOGs (below 1.70), group 1 had 15% at baseline, 23% at follow-up 1 and 33% at follow-up 2. Relative to group 1 the trend toward increased abnormality was noted in the higher dosage group 2 (24% at baseline, 44% at follow-up 1 and 44% at follow-up 2). However, 9% more of the higher dosage group were abnormal at baseline in contrast to their group 1 counterparts, suggesting a possible difference in the two populations.

We note that the ERG was considered since this test gives direct information about photoreceptor and inner retinal nuclear layer function, but requires a corneal electrode (we use Jet monopolar electrodes) that, in our hands, sometimes causes slight abrasions. In retrospect, however, with the large amount of EOG variability found in the patient population, the abnormal (acquired) color vision results and the requirement of active participation by the patient to successfully complete an EOG examination, we recommend ERG testing (especially at rod and cone threshold as well as 30 Hz pure cone stimulation) over an EOG.

Measurement of self-rated quality of vision is not frequently assessed in drug studies, but allows the patient to respond to the consequences of treatment decisions. In our simple determination of percent visual decrement (Table 4) there was a often a large difference between mean and median values, indicating that a few patients thought they had been markedly affected by the treatment and/or disease. An example of skewed data is evident in group 2 follow-up visit 1 where 44% (18 of 41) report no visual decrement, but 22% (nine of 41) state that they were greater than 40% impaired. Having a large range in the data implies that the questionnaire is sensitive to extremes in self-perception and further indicates that patients react to treatment differently. Two patients who reported greater than 65% visual decrement had only lost two lines of vision. They could have been hyper-sensitive to change or their quality of life may have suffered and they could no longer complete an important everyday task, e.g. ability to read small print. High decrement scores should be a red flag to the clinician, providing an opportunity to identify and possibly correct a self-perceived patient problem.

Conclusion

This study did not show a consistent statistical or trend toward increased visual complications in a group of patients with metastatic melanoma treated with a combination therapy of tirapazamine plus cisplatin. Nor was there a clear dose-response relationship. Objective fundus photos did not reveal macular changes associated with toxicity. We note that photo documentation was our most objective measure, but also the least sensitive. Visual acuity remained constant. While this treatment has no apparent ocular safety concerns, there are several limitations to this evaluation. In group 1 approximately one-third had brain metastases which had been treated by radiation and the number of patients in both groups who apparently improved their baseline EOGs and visual acuities at follow-up suggests that patient cooperation due to fatigue or illness can cause variation in the data, perhaps masking a significant effect. Also follow-up intervals were short due to poor patient survival. Subtle abnormalities may have become more obvious over time.

Evaluation of chemotherapy-related side effects is complex given that disease- and treatment-related factors may have overlapping symptomatology. In addition to tirapazmine-cisplatin therapy, these treated patients may have had vision changes due to brain metastasis or the drugs prescribed to control the complications of such spread. In addition, some patients had other conditions such as hypertension, diabetes, depression, migraine headache, primary eye disease, etc., and some of the medications prescribed for their therapy may be associated with vision complaints. A good proportion of these patients was receiving narcotic analgesics or anti-convulsive medications. The contribution of these palliative drugs to vision-related symptomatology experienced by these patients cannot be adequately differentiated from that due to tirapazamine-cisplatin chemotherapy.

Even thought we did not encounter extreme toxic reactions to the drug regimen under study, it is important to consider severe risks factors, even if rare. Unfortunately, the metastatic disease was the limiting factor in this study, preventing us from performing follow-up examinations on patients who did show

subtle abnormalities. Most patients were deceased or too ill to be re-examined in a rigorous fashion as the study required.

Acknowledgments

We thank Michael F Marmor MD and Sanofi-Winthrop Pharmaceutical for commenting on this manuscript.

References

1. Brown JM. SR 4233 (tirapazamine): a new anticancer drug exploiting hypoxia in solid tumours. *Br J Cancer* 1993; **67**: 1163–70.
2. Zeman EM, Brown JM, Lemmon MJ, Hirst VK, Lee WW. SR-4233: a new bioreductive agent with high selective toxicity for hypoxic mammalian cells. *Int J Radiat Oncol Biol Biophys* 1986; **12**: 1239–42.
3. Lartigau E, Guichard M. The effect of tirapazamine (SR-4233) alone or combined with chemotherapeutic agents on xenografted human tumours. *Br J Cancer* 1996; **73**: 1480–5.
4. Dorie MJ, Brown JM. Tumor-specific, schedule-dependent interaction between tirapazamine (SR 4233) and cisplatin. *Cancer Res* 1993; **53**: 4633–6.
5. Wilding G, Carusa R, Lawrence TS, Ostchega Y, Ballintin EJ, Young RC, Ozols. Retinal toxicity after high-dose cisplatin therapy. *J Clin Oncol* 1985; **3**: 1683–9.
6. Pippitt CH, Hyman BM, Homesley HD, Jacob VW. Cisplatin associated cortical blindness. *Gynecol Oncol* 1981; **12**: 253–5.
7. Miller DF, Bay JW, Lederman RJ, Purvis JD, Rogers LR, Tomsak RL. Ocular and orbital toxicity following intracarotid injection of BCNU (carmustine) and cisplatinum for malignant gliomas. *Ophthalmology* 1985; **92**: 402–6.
8. Khawly JA, Rubin P, Petros W, Peters WP, Jaffe GJ. Retinopathy and optic neuropathy in bone marrow transplantation for breast cancer. *Ophthalmology* 1996; **103**: 87–95.
9. Aylward JM. Hydroxychloroquine and chloroquine: assessing the risk of retinal toxicity. *J Am Optom Ass* 1993; **64**: 787–97.
10. Kato I, Watanabe J, Nakamura T, Harada K, Hasegawa T, Kanayama R. Mapping of brainstem lesions by the combined use of tests of visually-induced eye movements. *Brain* 1990; **113**: 921–35.
11. Pall H, Blake DR, Winyard P, *et al.* Ocular toxicity of desferrioxamine—an example of copper promoted auto-oxidative damage? *Br J Ophthalmol* 1989; **73**: 42–7.
12. De Laey JJ, De Rouck A, Priem H, Vanhoorne M. Ophthalmological aspects of chronic CS2 intoxication. *Int Ophthalmol* 1980; **3**: 51–6.
13. Weiss JN, Ochs AL, Abedi S, Selhorst JB. Retinopathy after tilorone hydrochloride. *Am J Ophthal* 1980; **90**: 846–53.
14. Marmor MF. Clinical electrophysiology of the retinal pigment epithelium. *Documenta Ophthalmologica* 1991; **76**: 301–13.
15. Kellner Um Kleine-Hartlage P, Foerster MH. Cone dystrophies: clinical and electrophysiological findings. *German J Ophthalmol* 1992; **1**: 105–9
16. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. *Am J Optom Physiol Optics* 1976; **53**: 740–5.
17. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; **94**: 91–6.
18. Holladay JT, Prager TC. Mean visual acuity. *Am J Ophthalmol* 1991; **111**: 372–4.
19. Prager T, Urso R, Holladay J, Stewart R. Glare testing in cataract patients: instrument evaluation and identification of sources of methodological error. *J Cataract Refractive Surg* 1989; **15**: 149–57.
20. Vingrys AJ, King-Smith PE. A quantitative scoring technique for panel tests of color vision. *Invest Ophthal Vis Sci* 1988; **29**: 50–63.
21. Atchison DA, Bowman KJ, Vingrys AJ. Quantitative scoring methods for D15 panel tests in the diagnosis of congenital color vision deficiencies. *Optom Vision Sci* 1991; **68**: 41–8.
22. Marmor MF, Zrenner E. Standard for clinical electro-oculography. International Society for Clinical Electrophysiology of Vision. *Arch Ophthal* 1993; **111**: 601–4.
23. Zonneveldt A, van Lith G. The electrooculogram and its interindividual and intraindividual variability. *Ophthalmologica* 1980; **181**: 165–9.
24. Alanko HI. Clinical electro-oculography. *Acta Ophthalmol* 1984; **61**: 139–48.
25. Krogh E. Normal values in clinical electrooculography. V. Variability within and between eyes. *Acta Ophthalmol* 1977; **55**: 986–93.

(Received 17 March 1998; revised form accepted 23 April 1998)