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Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review

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Background. The outcomes of patients with surgery- and radiation-refractory meningiomas treated with medical therapies are poorly defined. Published reports are limited by small patient numbers, selection bias, inclusion of mixed histologic grades and stages of illness, and World Health Organization (WHO) criteria changes. This analysis seeks to define outcome benchmarks for future clinical trial design.

Methods. A PubMed literature search was performed for all English language publications on medical therapy for meningioma. Reports were tabulated and analyzed for number of patients, histologic grade, prior therapy, overall survival, progression-free survival (PFS), and radiographic response.

Results. Forty-seven publications were identified and divided by histology and prior therapies, including only those that treated patients who were surgery and radiation refractory for further analysis. This included a variety of agents (hydroxyurea, temozolomide, irinotecan, interferon-α, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, imatinib, erlotinib, and gefitinib) from retrospective, pilot, and phase II studies, exploratory arms of other studies, and a single phase III study. The only outcome extractable from all studies was the PFS 6-month rate, and a weighted average was calculated separately for WHO grade I meningioma and combined WHO grade II/III meningioma. For WHO I meningioma, the weighted average PFS-6 was 29% (95% confidence interval [CI]: 20.3%–37.7%). For WHO II/III meningioma, the weighted average PFS-6 was 26% (95% CI: 19.3%–32.7%).

Conclusions. This comprehensive review confirms the poor outcomes of medical therapy for surgery- and radiation-refractory meningioma. We recommend the above PFS-6 benchmarks for future trial design.

Keywords: anaplastic meningioma, atypical meningioma, chemotherapy meningioma, malignant meningioma, meningioma.

The clinical course of meningiomas treated with systemic medical therapies is poorly defined. Reports of medical therapy for meningiomas suffer from many limitations, including small patient numbers, selection bias, and inclusion of a mixture of histologic grades and patients at various stages of illness from new diagnosis to multiple recurrences after surgery and/or various forms of radiation therapy (RT).[1] In addition, a variety of agents with different mechanisms of action have been examined. Importantly, there are no uniform response criteria or well-documented benchmarks regarding overall survival (OS), progression-free survival (PFS), or 6-month PFS (PFS-6) for recurrent meningioma. Additionally, the histology at the time of treatment may be unconfirmed (radiographic diagnosis only), and some tumors classified as World Health Organization (WHO) grade I on initial

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Table 1. Overall systemic therapies for meningioma

Agent/Regimen	Mechanism of Action	Author	Year	*n*	WHO Grade				Median PFS	PFS-6	Best Radiographic Response				
					n/a	I	II	III			SD	MR	PR	CR	PD
Hydroxyurea	Ribonucleotide reductase inhibitor	Schrell	1997[42]	4	–	3	–	1	–	–	1	1	2	0	0
Hydroxyurea	Ribonucleotide reductase inhibitor	Newton	2000[32]	17	–	16	1	–	80 wk	–	14	0	0	0	2
Hydroxyurea	Ribonucleotide reductase inhibitor	Mason	2002[29]	20	–	16	3	1	–	–	16	1	0	0	3
Hydroxyurea	Ribonucleotide reductase inhibitor	Rosenthal	2002[39]	15	–	10	5	–	–	–	11	0	0	0	2
Hydroxyurea	Ribonucleotide reductase inhibitor	Paus	2003[35]	1	–	1	–	–	22 mo+	–	1	0	0	0	0
Hydroxyurea	Ribonucleotide reductase inhibitor	Loven	2004[27]	12	–	8	4	–	13 mo	–	9	1	0	0	0
Hydroxyurea (with RT)	Ribonucleotide reductase inhibitor	Hahn	2005[19]	21	4	13	2	2	–	–	19	2	0	0	0
Hydroxyurea	Ribonucleotide reductase inhibitor	Weston	2006[46]	6	1	5	–	–	–	–	3	0	0	0	1
Hydroxyurea	Ribonucleotide reductase inhibitor	Swinnen	2009[25]	28	–	28	–	–	27 mo	–	20	0	0	0	6
Hydroxyurea	Ribonucleotide reductase inhibitor	Chamberlain	2011[7]	60	–	60	–	–	4 mo	10%	21	0	0	0	39
Hydroxyurea	Ribonucleotide reductase inhibitor	Chamberlain	2012[4]	35	–	–	22	13	2 mo	3%	15	0	0	0	20
Temozolomide	Alkylator	Chamberlain	2004[8]	16	–	16	–	–	5 mo	0%	13	0	0	0	3
Irinotecan	Topoisomerase 1 inhibitor	Chamberlain	2006[9]	16	–	16	–	–	4.5 mo	6%	12	0	1	0	3
Cyclophos + Adriamycin + vincristine (adjuvant CAV)	Combination cytotoxic chemotherapy	Chamberlain	1996[3]	14	–	–	–	14	4.6 y		12	0	2	0	0
Interferon-α	Immunomodulation	Kaba	1997[23]	6	–	2	1	3	–	–	6	0	0	0	0
Interferon-α	Immunomodulation	Muhr	2001[30]	12	2	6	1	3	–	–	–	–	–	–	–
Interferon-α	Immunomodulation	Chamberlain	2008[5]	35	–	35	–	–	7 mo	54%	26	0	0	0	9
Mifepristone (RU486)	Anti-progesterone	Grunberg	1991[18]	14	2	7	3	2	–	–	8	4	0	0	1
Mifepristone (RU486)	Anti-progesterone	Steven	2001[44]	80	–	80	–	–	10 mo (placebo was 12 mo)	–	–	–	–	–	–
Mifepristone (RU486)	Anti-progesterone	Grunberg	2006[17]	28	4	22	–	2	–	–	8	–	–	–	–
Megestrol acetate	Progesterone receptor agonist	Grunberg	1990[16]	9	–	8	–	1	–	–	6	0	0	0	3
Medroxy-progesterone acetate	Synthetic progesterone	Jaaskelainen	1986[20]	5	–	4	–	1	–	–	4	0	0	0	1
Tamoxifen	Anti-estrogen	Markwalder	1985[28]	6	–	–	–	–	–	–	5	0	1	0	0
Tamoxifen	Anti-estrogen	Goodwin	1993[12]	21	–	–	–	–	15.1 mo	–	–	–	–	–	–
Octreotide	Somatostatin analogue	Runzi	1989[40]	1	1	–	–	–	–	–	1	0	0	0	0
Octreotide	Somatostatin analogue	Garcia-Luna	1993[11]	3	–	2	–	1	–	–	3	0	0	0	0
Octreotide	Somatostatin analogue	Jaffrain-Rea	1998[21]	1	–	–	–	–	–	–	1	0	0	0	0
Octreotide	Somatostatin analogue	Johnson	2011[22]	11	–	3	3	5	17 wk	–	8	0	0	0	3
Sandostatin LAR	Somatostatin analogue	Chamberlain	2007[6]	16	–	8	3	5	5 mo	44%	5	0	5	0	6
Pasireotide LAR (SOM230C)	Somatostatin analogue	Norden	2011[2]	26	–	9	17		20 wk	29%	16	0	0	0	6
Imatinib	PDGFR TKI	Wen	2006[44]	1	–	–	–	–	–	–	–	–	–	–	–
Imatinib	PDGFR TKI	Wen	2009[45]	23	–	12	5	5	2 mo	29.4%	9	0	0	0	10
Erlotinib	EGFR TKI	Raizer	2010[37]	1	–	–	1	–	–	–	1	0	0	0	0
Erlotinib or gefitinib	EGFR TKI	Norden	2010[34]	25	–	8	9	8	10 wk	28%	8	0	0	0	17

Imatinib + hydroxyurea	PDGFR TKI + ribonucleotide reductase inhibitor	Reardon	2012[29]	21	–	8	9	4	7 mo	61.9%	–	–	–	–	–
Vatalanib (PTL-787)	VEGFR + PDGFR TKI	Raizer	2010[37]	21	–	–	14	7	–	37.5%	12	0	1	0	5
Sunitinib	VEGFR + PDGFR TKI	Kaley	2010[24]	36	–	–	30	6	5.2 mo	42%	25	0	1	1	8
Bevacizumab	Anti-VEGF antibody	Puchner	2010[36]	1	–	–	–	1	–	–	0	0	1	0	0
Bevacizumab	Anti-VEGF antibody	Goutagny	2011[13]	1	1	–	–	–	–	–	0	1	0	0	0
Bevacizumab + paclitaxel	Anti-VEGF antibody	Wilson	2012[47]	1	–	1	–	–	15 mo +	–	0	1	0	0	0
Bevacizumab	Anti-VEGF antibody	Lou	2012[26]	14	1	5	5	3	17.9 mo	85.7%	11	0	1	0	2
Bevacizumab	Anti-VEGF antibody	Nayak	2012[31]	15	–	–	6	9	26 wk	43.8%	13	2	0	0	0

Abbreviations: PDGFR, platelet-derived growth factor receptor; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; SD, stable disease; MR, minor response; PR, partial response; CR, complete response; PD, progressive disease. *Some numbers may not add up due to differences in number accrued vs number reported on or evaluable.

pathology may have transformed to a higher-grade tumor at the time of medical therapy initiation. Finally, with recently updated WHO criteria there are likely fewer grade I and more grade II meningiomas (due to stage migration), potentially altering interpretation of previous trials.

This analysis of currently available published studies of systemic therapy for recurrent meningioma is part of an effort to define common parameters and benchmarks to use for future clinical trial design. The goal is not to critique published studies or draw conclusions about efficacy of specific agents, but rather to describe the historical outcomes with systemic medical therapies. The objective of this review is to provide endpoint benchmarks for effectiveness for trials in recurrent meningioma that will improve and standardize new clinical trials of medical therapies in this disease.

Materials and Methods

A PubMed literature search was performed for all English language publications reporting on the use of chemotherapy or systemic therapy for the treatment of recurrent meningioma. All reports identified were initially tabulated with the number of patients, histologic grade, prior therapy, and outcome measures, including OS, PFS, PFS-6, and radiographic response. However, these survival outcomes were not uniformly available in all of the studies, and the only survival outcome measure that was available for all, either as reported or extracted from tables, was PFS-6. Studies were divided by histology, and only studies that treated patients who had failed prior radiation and surgery were selected. The only outcome measure that was reproducible across studies was PFS-6. In order to obtain a single historical benchmark, a weighted average was calculated across studies where the PFS-6 value from each study was weighted for the individual sample size of the study compared with the overall sample size.

The analysis characterizes the outcome of meningiomas that fail radiation and surgery and establishes a historical baseline from relatively homogeneous groups of patients for future studies. For medical treatment outcomes, we excluded studies that reported only radiographic response data.

Results

The results of all identified studies of medical therapies for recurrent surgery- and radiation-refractory meningioma are summarized in Table 1.[2–47] It is immediately apparent that there is marked heterogeneity in study design and patient inclusion, leading to challenges interpreting the literature and difficulty comparing treatments.

One major problem with interpreting the literature on medical therapies for recurrent meningioma is the inclusion of differing histologies in the reports. Therefore, studies were divided into 2 groups, one including patients with WHO grade I meningiomas only and one including WHO grades II and III meningiomas. WHO grades II and III meningiomas were grouped together, as these grades of meningioma were almost universally reported together, and consequently no further separation could be made between these tumor grades.

Table 2. WHO grade I meningioma

Agent/Regimen	Author	Year	WHO Grade		Prior Therapy	Median PFS (TTP)	PFS-6	Median OS	Best Radiographic Response of Evaluable patients				
			n/a	I					SD	MR	PR	CR	PD
Hydroxyurea	Schrell	1997[42]	–	3	3 prior surgery 2 prior RT	–	2/3	–	0	1	2	0	0
Hydroxyurea	Newton	2000[32]	4	13	13 prior surgery 7 prior RT 9 with POD pre-tx 1 atypical due to brain invasion	80 wk	–	–	14	0	0	0	2
Hydroxyurea	Mason	2002[29]	–	16	16 prior surgery 4 prior RT	NR	–	–	15	1	0	0	0
Hydroxyurea	Paus	2003[35]	–	1	None	22 mo+	–	22 mo+	1	0	0	0	0
Hydroxyurea	Loven	2004[27]	–	8	All prior surgery 6 prior RT	–	–	–	6	1	0	0	0
Hydroxyurea (with RT)	Hahn	2005[19]	–	13	All surgery None prior RT	–	–	–	11	2	0	0	0
Hydroxyurea	Weston	2006[46]	1	5	Not documented	–	–	–	3	0	0	0	1
Hydroxyurea	Swinnen	2009[25]	–	28	Not documented	27 mo	–	NR	20	0	0	0	6
Hydroxyurea	Chamberlain	2011[7]	–	60	All prior surgery (29 >1 op) All prior RT	4 mo	10%	–	21	0	0	0	39
Temozolomide	Chamberlain	2004[8]	–	16	All prior surgery All prior RT	5 mo	0%	7 mo	13	0	0	0	3
Irinotecan	Chamberlain	2006[9]	–	16	All prior surgery All prior RT	4.5 mo	6%	7 mo	12	0	1	0	3
Interferon-α	Kaba	1997[23]	–	2	All prior surgery 1 had RT	–	–	–	2	0	0	0	0
Interferon-α	Chamberlain	2008[5]	–	35	All prior surgery All prior RT 34 prior chemotherapy	7 mo	54%	8 mo	26	0	0	0	9
Mifepristone (RU486)	Steven	2001[44]	–	80	Not described, but prior surgery and RT for eligibility	10 mo	–	–	–	–	2	–	–
Megestrol acetate	Grunberg	1990[16]	–	8	All biopsy None had RT	–	5/8 62.50%	–	6	0	0	0	2
Medroxy-progesterone acetate	Jaaskelainen	1986[20]	–	4	All prior surgery	–	–	–	4	0	0	0	0
Octreotide	Garcia-Luna	1993[11]	–	2	All surgery	–	–	–	2	0	0	0	0
Octreotide	Johnson	2011[22]	–	3	All surgery 9/11 overall had RT	–	–	–	3	0	0	0	0
Sandostatin LAR	Chamberlain	2007[6]	–	8	Overall: 14/16 prior surgery 13/16 prior RT 12/16 prior chemo	–	3/7	–	2	0	3	0	3

Pasireotide LAR (SOM230C)	Norden	2011[2]	–	9	Overall: All prior surgery 22/26 prior RT	27 wk	50%	–	–	–	–	–
Imatinib	Wen	2009[45]	–	13	Overall: 1–8 surgery 0–5 RT	3 mo	45%	–	–	–	–	–
Erlotinib or gefitinib	Norden	2010[34]	–	8	Overall: All prior surgery 21/25 prior RT 8/25 prior chemotherapy	9 wk	25%	13 mo	–	–	–	–
Imatinib + hydroxyurea	Reardon	2012[29]	–	8	Overall 7/21 > 3 recurrences	13.9 mo	87.50%	66 mo	–	–	–	–
Bevacizumab	Loe	2012		5	3–7 prior treatments	12.2 mo	80%	–	–	–	–	–

Abbreviations: POD, progression of disease; tx, therapy; TTP, time to progression; SD, stable disease; MR, minor response; PR, partial response; CR, complete response; PD, progressive disease.

Another major problem with interpreting the literature is the inclusion of patients at various stages of their illness, ranging from newly diagnosed tumors to tumors that have recurred despite multiple surgeries and radiation treatments and, in some cases, multiple chemotherapy regimens. Therefore, only studies that included a majority of patients who failed both surgery and radiation were included in the analysis.

The heterogeneity of response criteria further adds to the difficulty of comparison across studies. Standard Macdonald criteria, which were defined for high-grade gliomas, define disease progression as a 25% increase in tumor burden; however, many studies did not define criteria as to what constituted progression prior to study entry.[48–50] Most studies report survival outcomes but not in uniform fashion, with some studies reporting median OS and others reporting median PFS or PFS-6. Progression-free survival at 6 months was the most uniform response metric, either reported specifically or extractable from tabulated patient outcomes. In addition, PFS-6 rate was the only method that could then be summed across studies allowing for a combined single historical value.

Radiographic response rate was recorded when available but not selected as the primary outcome measure, as this provided little insight into treatment outcome and additionally is hindered by the variety of measures of response assessment. In addition, when response was reported, the vast majority of patients manifested stable disease as the best response.

WHO Grade I Meningioma

The WHO grade I meningioma group (Table 2) is unique in having the only phase III study of chemotherapy reported to date. Mifepristone (RU486, an anti-progesterone agent) was investigated in a phase III double-blind randomized placebo-controlled trial.[44] However, this trial was reported in only abstract form, so the full details regarding patient characteristics, outcomes, and statistical analyses are not available, and the study has not yet been published after formal peer review. The trial included only patients with a pathologic diagnosis (surgery) who had failed RT (unless medically unsafe or patient refusal, a number not stated in the abstract). The only outcome reported was median PFS, which did not differ among the 80 treated patients (10 mo) and the 80 placebo patients (12 mo) ($P = .44$).

The remaining manuscripts are heterogeneous and summarized in Table 3 by survival outcomes. These studies generally reported patients who had failed prior surgery and RT. A variety of agents were used (hydroxyurea, temozolomide, irinotecan, interferon-α, octreotide analogues, and tyrosine kinase inhibitors, including imatinib, erlotinib, and gefitinib in addition to mifepristone), and included were retrospective studies, a pilot study, a phase II study, an exploratory arm of 2 phase II studies, and a phase III study. None of these studies reported clinically significant activity as defined by radiographic response and PFS. The majority lacked a statistical plan for comparison, did not have a historical control for comparison, or appeared unlikely to meet their predetermined endpoint or accrual and stopped early. For the purposes of this paper, these therapies were considered ineffective.

The primary outcome common to all but the phase III mifepristone study was PFS-6. Including only the prospective studies of temozolomide, irinotecan, interferon-α, Sandostatin long-

Table 3. Survival of WHO grade I meningiomas that failed surgery and RT

Agent/Regimen	Author (study type)	Registration Number	Year	WHO Grade		Prior Therapy	Response Criteria	Median PFS (TTP)	PFS-6	Median OS
				n / a	I					
Hydroxyurea	Schrell (retrospective)	–	1997[42]	–	3	3 prior surgery 2 prior RT	Defined percent change	–	2/3 67%	–
Hydroxyurea	Chamberlain (retrospective)	–	2011[7]	–	60	All prior surgery (29 >1 op) All prior RT	Macdonald	4 mo	10%	–
Temozolomide	Chamberlain (phase II)	–	2004[8]	–	16	All prior surgery All prior RT	Macdonald	5 mo	0%	7 mo
Irinotecan	Chamberlain (phase II)	–	2006[9]	–	16	All prior surgery All prior RT	Macdonald	4.5 mo	6%	7 mo
Interferon-α	Chamberlain (phase II)	–	2008[5]	–	35	All prior surgery All prior RT 34 prior chemotherapy	Macdonald	7 mo	54%	8 mo
Mifepristone (RU486)	Steven (phase III)	–	2001[44]	–	80	Prior surgery and RT for eligibility	Not defined	10 mo	–	–
Sandostatin LAR	Chamberlain (pilot)	–	2007[6]	–	8	Overall: 14/16 prior surgery 13/16 prior RT 12/16 prior chemo	Macdonald	–	3/7 43%	–
Pasireotide LAR (SOM230C)	Norden (phase II)	NCT00859040	2011[2]	–	9	Overall: All prior surgery 22/26 prior RT	Macdonald	27 wk	50%	–
Imatinib	Wen (phase II)	NCT00045734	2009[45]	–	13	Overall: 1–8 surgery 0–5 RT	Macdonald	3 mo	45%	–
Erlotinib or gefitinib	Norden (exploratory arm of phase II)	NCT00045110 NCT00025675	2010[34]	–	8	Overall: All prior surgery 21/25 prior RT 8/25 prior chemotherapy	Macdonald	9 wk	25%	13 mo

Abbreviation: TTP, time to progression.

Table 4. WHO grade II/III meningioma

Agent/Regimen	Author	Year	WHO Grade		Prior Therapy	Group	Median PFS	PFS-6	Med OS	Best Radiographic Response of Evaluable Patients				
			II	III						SD	MR	PR	CR	PD
Hydroxyurea	Schrell	1997[42]	–	1	Failed surgery and RT	WHO III	–	1/1	–	1	0	0	0	0
Hydroxyurea	Newton	2000[32]	1	–	?		?	?	?	?	?	?	?	?
Hydroxyurea	Mason	2002[29]	3	1	All >1 surgery	WHO II	19 wk	1/3	–	2	0	0	0	1
					All prior RT	WHO III	4 wk	0/1	–	0	0	0	0	1
Hydroxyurea	Loven	2004[27]	4	–	All surgery 0 had prior RT	WHO II	–	–	–	3	0	0	0	0
Hydroxyurea (with RT)	Hahn	2005[19]	2	2	All surgery None prior RT	II/III	13 mo	–	–	4	0	0	0	0
Hydroxyurea	Chamberlain	2012[4]	22	13	All prior surgery All prior RT	Overall	2 mo	3%	II–8 mo III–6 mo	15	0	0	0	20
Cyclophos + Adriamycin + vincristine (adjuvant CAV)	Chamberlain	1996[3]	–	14	Adjuvant tx after surgery and RT 4 GTR, 10 STR	WHO III	4.6 y	–	5.3 y	8	0	2	0	0
Interferon-α	Kaba	1997[23]	1	3	All prior surgery All prior RT	II/III	–	–	–	4	0	0	0	0
Megestrol acetate	Grunberg	1990[16]	–	1	Prior surgery, RT, and chemotherapy	III	2 mo	0/1	–	0	0	0	0	1
Medroxy-progesterone acetate	Jaaskelainen	1986[20]	–	1	Prior surgery	III	–	–	–	0	0	0	0	1
Octreotide	Garcia-Luna	1993[11]	–	1	biopsy	III	6 wk	–	–	1	0	0	0	0
Octreotide	Johnson	2011[22]	3	5	All surgery	II	–	–	–	3	0	0	0	0
					9/11 overall had RT	III	–	–	–	2	0	0	0	3
Sandostatin LAR	Chamberlain	2007[6]	3	5	Overall: 14/16 prior surgery	II	–	0/2	–	1	0	1	0	1
					13/16 prior RT 12/16 prior chemo	III	–	2/5	–	1	0	1	0	3
Pasireotide LAR (SOM230C)	Norden	2011[2]	17		Overall: All prior surgery 22/26 prior RT	II/III	26 wk	20%	–	–	–	–	–	–
Imatinib	Wen	2009[45]	5	5	Overall: 1–8 surgery 0–5 RT	II/III	2 mo	0%	–	–	–	–	–	–
Erlotinib	Raizer	2010[37]	1	–	Not discussed	II	–	–	–	1	0	0	0	0
Erlotinib or gefitinib	Norden	2010[34]	9	8	Overall: All prior surgery 21/25 prior RT 8/25 prior chemotherapy	II/III	16 wk	29%	33 mo	–	–	–	–	–
Imatinib + hydroxyurea	Reardon	2012[29]	9	4	Overall 7/21 > 3 recurrences	II/III	5.3 mo	46.20%	20.9 mo	–	–	–	–	–
Vatalanib (PTL-787)	Raizer	2010[51]	14	7	All prior surgery	All	–	37.50%	–	12	0	1	0	5
					All prior RT	II	3.7 mo	–	22.9 mo	–	–	–	–	–
						III	3.6 mo	–	19.6 mo	–	–	–	–	–

Continued

Table 4. *Continued*

Agent/Regimen	Author	Year	WHO Grade		Prior Therapy	Group	Median PFS	PFS-6	Med OS	Best Radiographic Response of Evaluable Patients				
			II	III						SD	MR	PR	CR	PD
Sunitinib	Kaley	2010[24]	30	6	All prior surgery All prior RT	II/III	5.2 mo	42%	24.6 mo	25	–	1	1	8
Bevacizumab	Puchner	2010[36]	–	1	Prior surgery + RT	III	–	–	–	0	0	1	0	0
Bevacizumab	Loe	2012	5	3	1–7 prior treatments	II/III	15.8 mo	87.50%	–	–	–	–	–	–
Bevacizumab	Nayak	2012[31]	6	9	All prior surgery All prior RT	II/III	26 wk	43.80%	15 mo	13	2	0	0	0

Abbreviations: Cyclophos, cyclophosphamide; GTR, gross total resection; STR, subtotal resection; SD, stable disease; MR, minor response; PR, partial response; CR, complete response; PD, progressive disease; tx, therapy.

acting release (LAR), pasireotide LAR, imatinib, erlotinib, and gefitinib in patients who had failed surgery and RT, the weighted average PFS-6 rate was 29% (range 0%–54%; 95% confidence interval [CI]: 20.3%–37.7%).[2,5,6,8,9,34,45] If the 2 retrospective studies reporting on hydroxyurea were included, the weighted average PFS-6 dropped to 23% (range 0%–67%; 95% CI: 16.6%–29.4%).[7,42]

Median PFS and median OS are less frequently reported. For 8 papers with data available, patients receiving some form of medical therapy after failure of surgery and radiation had a median PFS ranging from 9 to 30.4 weeks.[2,5,7–9,34,43,45] In the 4 manuscripts with data available, median OS ranged from 7 to 13 months.[5,8,9,34] The single phase III trial reported a median PFS of 10 months.[43] Notably, the longest OS reported is derived from the combined erlotinib/gefitinib paper, a study that recruited very few patients, stopped early, and demonstrated no difference in outcome in patients with WHO grade I meningioma compared with WHO combined grade II/III meningioma.

In summary, these data suggest that patients with WHO grade I meningioma who fail surgery and RT and receive medical or systemic therapy have poor survival outcomes. Progression-free survival at 6 months is the most uniform outcome reported, with various studies reporting PFS-6 rates ranging from 0% to 67%. Combining all of these patients from retrospective and prospective studies, the weighted average PFS-6 rate is 23%; combining only the prospective studies, the weighted average PFS-6 rate is 29%. The only phase III data suggest a median PFS of 10 months, but this study was performed years ago and is reported only in abstract, rendering generalization of these data challenging. In conclusion, the current analysis suggests use of a PFS-6 benchmark of 29%, ignoring the prospective phase III mifepristone data for the reasons noted above. This analysis confirms the aggressive nature of surgery- and radiation-refractory recurrent WHO grade I meningioma.

WHO Grade II/III Meningioma

The natural history of WHO grades II and III meningiomas that have failed surgery and RT is also challenging to interpret in the available literature (Table 4). No phase II or phase III study restricted to this patient population has been completed and published aside from abstracts. The recent phase II studies of sunitinib, pasireotide LAR, and vatalanib are completed, and publication is expected in the near future.[2,24,51]

Only those studies of patients who have failed surgery and RT are summarized in Table 5. These studies represent a heterogeneous group of treatments and trial designs, including phase II studies, exploratory arms of other studies, retrospective reports, and case studies. These trials used a variety of agents, including hydroxyurea, megestrol acetate, octreotide analogues, bevacizumab, and tyrosine kinase inhibitors. Importantly, there is no completed phase III study in this patient population. Combining these studies including prospective and retrospective studies and possibly active agents, patients treated with some form of systemic therapy at the time of radiation failure have a PFS-6 ranging from 0% to 64% with a weighted average PFS-6 of 26% (95% CI: 19.3%–32.7%).

A North American Brain Tumor Consortium (NABTC) phase II study of the platelet-derived growth factor receptor tyrosine kinase inhibitor imatinib, terminated prematurely due to slow

Table 5. Survival of WHO grade II and III meningioma that failed surgery and RT

Agent/Regimen	Author (study type)	Registration Number	Year	WHO Grade		Response Criteria	Prior Therapy	Group	Median PFS	PFS-6	Median OS
				II	III						
Hydroxyurea	Schrell (retrospective)	–	1997[42]	–	1	Defined percent change	Failed surgery and RT	WHO III	–	1/1	–
Hydroxyurea	Mason (retrospective)	–	2002[29]	3	1	Macdonald	All >1 surgery	WHO II	19 wk	1/3	–
							All prior RT	WHO III	4 wk	0/1	-
Hydroxyurea	Chamberlain (retrospective)	–	2012[4]	22	13	Macdonald	All prior surgery All prior RT	Overall	2 mo	3%	II–8 mo III-6 mo
Megestrol acetate	Grunberg (retrospective)	–	1990[16]	–	1	Not defined	Prior surgery, RT, and chemotherapy	III	2 mo	0/1	–
Sandostatin LAR	Chamberlain (pilot)	–	2007[6]	3	5	Macdonald	Overall: 14/16 prior surgery 13/16 prior RT 12/16 prior chemo	II III	– –	0/2 2/5	– –
Pasireotide LAR (SOM230C)	Norden (phase II)	NCT00859040	2011[2]	17		Macdonald	Overall: All prior surgery 22/26 prior RT	II/III	26 wk	20%	–
Imatinib	Wen (phase II)	NCT00045734	2009[45]	5	5	Macdonald	Overall: 1–8 surgery 0–5 RT	II/III	2 mo	0%	–
Erlotinib or gefitinib	Norden (exploratory arm of phase II)	NCT00045110 NCT00025675	2010[34]	9	8	Macdonald	Overall: All prior surgery 21/25 prior RT 8/25 prior chemo	II/III	16 wk	29%	33 mo
Vatalanib (PTL-787)	Raizer (phase II)	NCT00348790	2011[51]	14	7	Macdonald	All prior surgery All prior RT	II III	7.6 mo 3.6 mo	64.30% 37.50%	26 mo 23 mo
Sunitinib	Kaley (phase II)	NCT00589784	2010[24]	30	6	Macdonald	All prior surgery All prior RT	II/III	5.2 mo	42%	24.6 mo
Bevacizumab	Nayak (retrospective)	–	2012[31]	6	9	RANO	All prior surgery All prior RT	II/III	26 wk	43.80%	15 mo

Table 6. PFS-6 analysis of WHO grade II and III meningioma that failed surgery and RT

Drug	Design	*n*	PFS-6
Including all agents (hydroxyurea, megestrol acetate, Sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib, and bevacizumab)	Retrospective reports, pilot study, phase II trials	164	26%
Including all agents except the case reports	Retrospective reports, pilot study, phase II trials	158	25%
Including all agents except the potentially active drugs (ie, excluding bevacizumab, sunitinib, and vatalanib)	Retrospective reports, pilot study, phase II trials	92	14%
Including only negative phase II studies (imatinib and SOM230C)	Phase II	27	11%

Table 7. Survival outcome estimates for medical treatment after surgery and radiation failure

	Median PFS	PFS-6	Median OS
WHO grade I meningioma			
Phase III data	10 mo	–	–
All prospective trials	9–30.4 wk	29%	7–13 mo
All reports (prospective + retrospective)	9–30.4 wk	23%	7–13 mo
WHO grade II and III meningioma			
Imatinib	2 mo	0%	–
All negative reports (prospective + retrospective)	1–6 mo	14%	6–33 mo
All reports (prospective + retrospective + possibly active agents)	1–6 mo	26%	6–33 mo

accrual and lack of response, was arguably the best designed prospective trial.[45] Therefore, although its statistical criteria were not met, it suggested that imatinib is an ineffective drug, with a median PFS of 2 months and PFS-6 of 0% (it is important to note that this included only 10 patients). This may reflect the natural history of essentially untreated radiation- and surgery-refractory recurrent grade II/III meningiomas. Other prospective studies include the somatostatin analogues (both the Sandostatin LAR pilot study and the pasireotide LAR phase II study) and the NABTC phase II studies of erlotinib and gefitinib in malignant glioma that enrolled patients with recurrent meningioma to an exploratory arm. These studies report PFS-6 rates of 20%–29% in surgery- and RT-refractory high-grade meningioma.

The activity of these drugs is uncertain. For the patients enrolled in most of these trials, such treatments were deemed ineffective. Therefore, if we exclude from our analysis the sunitinib, vatalanib, and bevacizumab trials in which treatment appears to have some activity, the PFS-6 rate for patients treated with hydroxyurea, megestrol acetate, Sandostatin LAR, pasireotide LAR, imatinib, erlotinib, and gefitinib is 14% (95% CI: 6.9%–21.1%).[2,4,6,16,29,34,42,45] These results are summarized in Table 6.

Other survival outcomes are more difficult to ascertain from these studies. For publications with data available, patients receiving some form of medical therapy after failure of surgery and radiation had a median PFS ranging from 4 weeks to 26 weeks.[2,4,6,16,29,34,35,45] This patient population had a median OS ranging from 6 months to 33 months.[4,34]

One additional challenge to interpreting these data is that this report includes outcomes of the combined group including both WHO grades II and III tumors. It is quite possible, and arguably likely, that the outcomes differ according to WHO grade. Where available, stratification by grade II versus III is presented in Table 5. However, the overall numbers are very low.

In summary, currently available data suggest that patients with WHO grades II and III meningioma who fail surgery and RT and receive medical therapy have very poor survival outcomes. PFS-6 is the most uniform outcome to report, with various studies reporting PFS-6 rates ranging from 0% to 64%. The most conservative approach to the natural history of these tumors is a PFS-6 rate of 0% based upon the prospective phase II imatinib trial. Combining all studies and patients together, including inactive therapies, active agents, retrospective and prospective studies, and both histologies, the overall PFS-6 rate is 26% (95% CI: 19.3%–32.7%), similar to the summed value seen with surgery- and radiation-refractory recurrent grade I meningioma.

Discussion

Our comprehensive review of the available literature confirms the poor clinical outcome of recurrent meningiomas that have failed surgery and RT and have been subsequently treated with chemotherapy or other systemic agents. PFS-6 is the most consistently recorded endpoint in these various studies. The considerable heterogeneity in these studies, in addition to the patient selection bias, limits our conclusions, notwithstanding our attempt to homogenize the published literature as best as possible (Table 7).

Upon analysis of the literature, multiple limitations pervade a meaningful comparison across studies, in addition to the heterogeneity discussed above. First, no studies have any criteria on the growth rate of the tumors prior to treatment, which is compounded by the lack of uniform time points of imaging for detection of tumor progression. Most variability occurs between using a 2-month imaging interval and a 3-month imaging interval, which is unlikely to alter the 6-month statistics; however, the growth rate may cause discrepancies. The growth rate may also account

Table 8. PFS-6 benchmarks for future studies

PFS Rate	WHO Grade I	WHO Grade II and Grade III
Benchmark	29%	26%
Rate not of interest	<40%	<30%
Rate probably of interest	>50%	>35%

for the similarity in results of the grade I and grade II/III groups, and authors should include this parameter to help us better interpret future study results. A second issue that may affect these results is the lack of uniform criteria for documenting true tumor progression after multiple radiation treatments in order to exclude patients who actually have radiation necrosis. This may affect not only the "negative" studies in which drugs were deemed ineffective, but also the anti-angiogenic therapy studies in which the therapy may have an effect on necrosis itself. Third, the reporting of survival outcomes such OS and PFS was rather poor. Therefore, we are unable to correlate PFS with OS to determine whether PFS is truly a surrogate for OS and an ideal endpoint. Finally, our study is limited by publication bias, as we included only peer-reviewed literature from PubMed. Therefore, we may have missed negative studies that were never published in full or those published in only meeting abstracts.

Using the collated tables included herein, there are several different benchmarks that can be used at the discretion of the investigators, goals of the study, and tumor histology. However, to limit overstating the benefit of ineffective therapies, the Revised Assessment in Neuro-Oncology (RANO) working group recommends the following suggestions (Table 8) for single arm or phase II studies. For WHO grade I meningioma, consider powering future trials against a PFS-6 rate of 29%, with PFS-6 <40% probably not of interest. For WHO grade II/III meningiomas, future trials should be powered against a PFS-6 of 26%, with PFS-6 <30% probably not of interest. Of course, how high or low to set the bar is at the discretion of each investigator and study, but this should be reported in each study to allow broader interpretation of positive and negative results. These may also change as more information is learned, particularly about pretreatment growth rates, which may provide better subgroups than WHO grade. Radiographic responses are very uncommon, although currently it is unclear whether this is an effect of tumor biology or ineffective therapy. Additionally, the growth rate of meningiomas is quite variable and may need consideration as well. For comparative trials and specifically phase III trials, investigators may prefer other endpoints—such as survival—that may be more feasible in that setting.

What is very clear from these data is that as a field we need to improve and standardize not only the historical comparisons but the data that are reported, which should include PFS and OS, prior therapies, and probably pretreatment growth rate. A future RANO manuscript in preparation will specifically address meningioma response criteria and attempt to address some of these issues.

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