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Anaplastic Astrocytoma

*Sean A. Grimm, MD**
Thomas J. Pfiffner, MD

Address
*Department of Neurology, University of Minnesota School of Medicine, 420 Delaware Street SE, MMC 295, Minneapolis, MN 55455, USA
Email: sgrimm@umn.edu

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Opinion statement

Standard treatment of anaplastic astrocytoma (AA) in good performance patients consists of maximal safe surgical resection followed by focal, fractionated, external beam radiotherapy (RT) alone or in combination with concurrent and adjuvant temozolomide (TMZ). Since prospective data regarding the use of chemoradiotherapy for AA is lacking, the practice is based on the extrapolation of results from a randomized study in glioblastoma (GB). Whether the data from the GB study can and should be extrapolated is controversial, although a large multicenter, randomized, phase III study is underway to define optimal initial AA treatment. Patients should be tapered off corticosteroids completely or to the lowest dose necessary to treat neurologic dysfunction. Anti-epileptic drugs (AED) are not indicated unless there is a history of seizure; levetiracetam is the preferred AED in malignant glioma (MG). Unless there is evidence of intracranial hemorrhage, venous thromboembolism (VTE) should be treated with low-molecular-weight heparin (LMWH) therapy. At recurrence, patients with good performance status are usually treated with cytotoxic chemotherapy following, or in lieu of, repeat surgery. TMZ is the preferred chemotherapeutic agent in patients without prior exposure; lomustine is recommended for tumors resistant to TMZ. In patients with neurologic dysfunction secondary to tumor edema and mass effect who are not amenable to surgery, the use of bevacizumab is associated with improved neurologic function and better quality of life. Given the limited treatment options at tumor recurrence, consideration for enrollment on a clinical trial is encouraged.

Introduction

AA is a malignant glioma (MG) with mean age of onset of 41 years [1]. In population-based registries, it constitutes 4 % of all malignant nervous system tumors [1] and 10 % of all gliomas [2]. The prognosis for patients with AA can be variable although it is generally poor. Despite treatment, median survival and the 5-year survival rate are 3 years and 28 %, respectively [3, 4]. Although AA may arise as a new primary "de novo" tumor, 75 % result from dedifferentiation of a lower-grade astrocytoma [5]. Exposure to ionizing

radiation and rare genetic syndromes such as neurofibromatosis types 1 and 2, tuberous sclerosis, and Li-Fraumeni are the only established causes of AA. Various occupational and environmental exposures have been suggested by some investigators, although evidence is lacking [6–9].

AA presents with localized or generalized neurological signs and symptoms, which are determined by the neuro-anatomical location of the tumor. Generalized signs and symptoms consist of headache, seizures, and personality change. Compared with low grade glioma, seizures are less common; seizures were the presenting symptom in 46 % of AA in 1 study [10]. Localized signs and symptoms include focal weakness, sensory symptoms, gait ataxia, visual symptoms, and language dysfunction.

Magnetic resonance imaging (MRI) with administration of gadolinium contrast is the optimal non-invasive technique for the diagnosis and management of AA [11, 12]. MRI is useful to establish a differential diagnosis, guide tumor biopsy or resection, plan radiotherapy, and monitor response to treatment and diagnose disease progression [13]. Head computerized tomography (CT) scan and non-contrast MRI are not adequate for thorough evaluation, but CT must suffice for those unable to undergo an MRI.

On MRI, AA presents as an ill-defined T1-weighted hypointense and T2-weighted hyperintense mass with associated vasogenic edema. Typically, nodular areas of gadolinium enhancement are present, although up to one third of tumors may show no contrast enhancement [5, 14]. The presence of abnormal enhancement in a tumor implies the presence of a high-grade tumor even if a biopsy shows a low-grade tumor as sampling error may occur. Additional advanced imaging techniques such as Diffusion-Weighted Imaging, proton MR spectroscopy, and MR perfusion may aid in the diagnosis and management of AA [5, 14, 15].

AA often displays heterogeneous histology, consisting of distinct areas of low and high grade tumor, which is thought to indicate biologic progression from a lower grade precursor. Since the diagnosis is sometimes determined from small biopsy tissue specimens, sampling error may occur [16]. The World Health Organization (WHO) classification scheme is the most widely used system of grading glial tumors. AA, defined as a grade III glioma, is characterized by increased mitotic activity, marked cellularity, and nuclear atypia, whereas necrosis or extensive microvascularization are absent [12, 17]. The MIB-1 labeling index is usually 5 % to 10 %, but may overlap with low grade astrocytoma or GB, and show considerable variation within a given tumor [18–21].

There is no single molecular marker that defines AA, although mutations in TP53 are frequent, and differentiate AA from oligodendroglial tumors. The Cancer Genome Atlas GB project has resulted in a tremendous influx of new data concerning the genomic alterations in gliomas [22, 23, 24•]. The data relates primarily to primary (de novo) GB, although a small number of secondary tumors were included. AA is thought to share a common lineage and thus molecular pathology with secondary GB [25, 26]. Utilizing gene expression profiling, Phillips et al. identified novel subgroups of high grade glioma (*Proneural, Proliferative, and Mesenchy*mal) defined by distinct clinical and molecular characteristics [27]. Nearly all AA tumor specimens and good prognosis GB were classified as *Proneural*. The *Proneural* subtype had the best prognosis and expresses genes associated with normal brain processes and neurogenesis rather than gene expression indicative of cell proliferation and angiogenesis that are found in the other 2 subtypes. The relevance of these subtypes to treatment is yet to be determined.

Epigenetic silencing of the O^6 –methyl-guanyl-methyl-transferase (MGMT) DNA repair gene by promoter methylation has been associated with longer survival for GB patients, particularly those treated with alkylating agents such as TMZ [28–30]. Much less is known about the prognostic value of MGMT methylation in AA. A retrospective study demonstrated MGMT promoter methylation in 54.7 % (35 of 64 patients) of AA [31]. The median survival of WHO grade III gliomas with a methylated MGMT promoter showed a trend in longer survival, although it was not statistically significant (9.7 vs 6.1 years, P=0.33). The authors concluded that MGMT failed to demonstrate a prognostic or predictive role although the study was confounded by the fact that only one third of patients were treated with TMZ after malignant progression and another quarter did not receive any adjuvant chemotherapy.

Wick et al. analyzed the MGMT promoter methylation status in 202 evaluable WHO grade III gliomas treated on a randomized phase III trial.[32] MGMT promoter methylation was detected in 50 % (48 of 96) of AA. MGMT promoter methylation was associated with better progression free survival (PFS) regardless of whether patients were treated with alkylating

chemotherapy agents or RT alone. The authors concluded that MGMT promoter hypermethylation in anaplastic gliomas may be regarded as a prognostic marker for good outcome in patients treated with radiotherapy or predictive for response to radiotherapy itself. They speculated that MGMT hyper-methylated anaplastic gliomas may carry a general defect in regulation of DNA methylation leading to epigenetic inactivation of multiple genes, including genes linked to radio-resistance.

Somatic mutations of the isocitrate dehydrogenase enzymes (IDH1 and IDH2) appear to play a critical role in the pathogenesis of most AA and secondary GB [23, 24•, 33•, 34]. The IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate, a key component of the Krebs cycle [33•]. The enzymes utilize NADP + as a cofactor to generate α-ketoglutarate and NADPH in a reversible reaction. Over 90 % of the IDH mutations in gliomas affect IDH1 [34]. The IDH1 mutations target specific arginine residues and are exclusively heterozygous raising the possibility of a novel gain-of-function phenotype whereby the mutant enzymes produce high levels of what is ordinarily a minor metabolic product, R(-)-2-hydroxyglutarate, with relative depletion of α-ketoglutarate and NADPH [23, 24•, 34–36]. Whether there is a role of 2-hydroxglutarate in tumor development is unknown.

It is unknown whether therapy targeting IDH mutations would be beneficial. Studies have demonstrated that the IDH mutation is a positive prognostic factor independent of age, functional status, and MGMT promoter methylation status [32]. In fact IDH1 may be a better predictor of prognosis than histology. Patients with IDH1 wild type AA had worse prognosis than IDH1-mutated GB in one study [37•]. It is anticipated that IDH status will be an important consideration in future revisions of the WHO criteria for gliomas.

Treatment

Pharmacologic treatment: supportive care

- Seizures, brain edema, and deep venous thrombosis are common medical issues encountered in brain tumor patients.
- AA patients with history of seizure should be treated with an AED. The use of prophylactic AED in brain tumor patients is controversial. The American Academy of Neurology issued a practice guideline advising that AED should not be used in brain tumor patients who have never experienced a seizure because of the lack of beneficial evidence [38].
- Antiepileptic drugs that induce hepatic cytochrome p-450 enzymes, such as phenytoin, carbamazepine, oxcarbamazepine, and phenobarbital, should be avoided because of interactions with many chemotherapeutic agents and other drugs. Although only approved by the FDA as add-on therapy, single agent levetiracetam is the most widely used, well tolerated, and best agent for brain tumor patients [39, 40] (class III) Other "non-enzyme inducing" AED include gabapentin, lacosamide, lamotrigine, topiramate, valproic acid, and zonisamide.
- Corticosteroids reduce brain tumor associated vasogenic edema through restoration of the blood-brain-barrier via an unknown mechanism [41]. Reduction of vasogenic brain edema may improve neurologic dysfunction. Asymptomatic patients with brain edema do not need prophylactic corticosteroids. Because of their numerous side effects, patients should be treated with the lowest dose of corticosteroid that controls their symptoms and every effort should be

made to discontinue the drug completely. For mostly historical reasons, dexamethasone is the most widely used corticosteroid in Neuro-Oncology [41].

- Venous thromboembolism (VTE) is common in malignant glioma [42]. Prospective clinical trials report an annual risk of 17 %–22.9 % [43–45]. Venous ultrasound and CT angiography are the diagnostic imaging modalities of choice for the diagnosis of deep venous thrombosis and pulmonary embolism, respectively. To reduce the risk of post-operative VTE, prophylactic low molecular weight heparins (LMWH) should be started on the day after craniotomy. There is no indication for prophylactic anticoagulation beyond the post-operative period. Despite the fear of intracranial hemorrhage, the treatment of VTE disease with full therapeutic anticoagulation appears to be safe for primary brain tumor patients [42], (class IV). Compared to warfarin, LMWH may be safer and more effective and is preferable because of minimal drug and food interactions and lack of requirement for laboratory monitoring [46], (class IV). The use of therapeutic anticoagulation is not contraindicated in patients receiving anti-vascular endothelial growth factor (VEGF) therapy with bevacizumab [47], (class II). Because of their high complication rate, inferior venae cava filters are only recommended for patients with VTE disease and significant intracranial hemorrhage or some other anti-coagulation contraindication [48], (class IV).

Levetiracetam

Standard dosage	500–1500 mg by mouth twice a day.
Contraindications	Hypersensitivity to levetiracetam.
Main drug interactions	No significant drug interactions [49]. Specific to AA, there are no known drug interactions with corticosteroids, warfarin, LMWH, or chemotherapeutic agents.
Main side effects	The most common side effects include somnolence, asthenia, and dizziness. Behavioral abnormalities such as irritability, aggression and psychosis are less common. All AED may cause an increase in suicidal thoughts.
Special points	Anti-epileptic drug of choice for neuro-oncologic patients. The dosage should be reduced in patients with impaired renal function.
Cost	Moderate.

Dexamethasone

Standard dosage	In patients with symptomatic brain edema, start at 8 mg twice daily, tapering the dose to tolerance at a rate of 2 mg every 4 days. If 16 mg per day are ineffective, the dose can be doubled every 48 hours until there is maximal response.
Contraindications	Systemic fungal infection or hypersensitivity to dexamethasone.
Main drug interactions	Dexamethasone has been reported to increase and decrease phenytoin levels leading to alteration of seizure control. Phenytoin may reduce effective

concentrations of dexamethasone. Co-administration with warfarin usually results in inhibition of response to warfarin so that coagulation indices should be monitored closely.

Main side effects Common side effects include insomnia, tremor, weight gain, steroid myopathy (weakness of neck flexors and muscles of the shoulder and pelvic girdle), diabetes, behavioral changes (hyperactivity and irritability), urinary frequency (nocturia), and hiccups. Less common but serious side effects include osteoporosis, avascular necrosis of the hip, gastrointestinal (GI) bleeding, perforation of the GI tract, psychosis, depression, opportunistic infections (Pneumocystis), glaucoma, delirium, and pancreatitis [41].

Special points Gastric protection with H2 blockers or proton pump inhibitors is not recommended unless a patient develops upper GI symptoms or there is history of gastric ulceration or evidence of bleeding. Patients treated with corticosteroids for longer than 6 weeks should receive prophylactic trimethoprim-sulfamethoxazole 3 times per week; the drug is continued until a month after corticosteroids are stopped [41], (class IV).

Cost Inexpensive.

Tumor treatment at diagnosis

Surgery

- Maximal safe surgical resection is recommended for high performance patients, although there has never been a prospective, randomized study to demonstrate an advantage over biopsy. Retrospective analyses suggest improved overall survival (OS) with more extensive surgical resection [4, 32], (class IV). Extensive resection also has the benefit of providing adequate tissue for histological diagnosis and reduces tumor mass effect which may improve neurologic dysfunction.
- Surgery is not curative because of diffuse infiltration of tumor into the surrounding brain parenchyma.
- Advances in neuroimaging have improved the ability to maximally resect tumor while minimizing adverse effects. Functional MRI and Diffusion Tensor Imaging allow localization of eloquent brain areas and white matter tracts, respectively, so that these areas can be avoided during tumor resection. Intraoperative MRI is used to depict residual tumor tissue during an operation, aiding neurosurgeons in achieving gross total resection [5, 50–52], (class IV).

Radiation Therapy (RT)

- Following surgical resection, RT is standard treatment for MG. The benefit of RT was established in multiple prospective clinical studies [53–60], (class III).
- RT is not curative because of the potential damage to the normal nervous system at the high radiation doses that would be required to sterilize the tumor [41].
- The use of stereotactic radiosurgery boost in addition to standard RT failed to show benefit for newly diagnosed MG in randomized clinical trials [61].

- Accelerated hyperfractionation radiotherapy (70.4 Gy in 44 fractions delivered twice daily) was equivalent to standard fractionated RT (total dose 59.4 Gy) [62], (class III).

RT

Standard procedure RT is delivered to the contrast enhancing tumor plus the T2-weighted peritumoral surround and a 3 cm margin. This planned tumor volume receives approximately 50 Gray (Gy). The contrast enhancing tumor volume receives an additional 10 Gy; all administered in 18–20 Gy fractions per day, 5 fractions per week, for a total of 60 Gy.

Contraindications There are no definitive contraindications, although elderly patients with poor performance status may have difficulty tolerating the therapy.

Complications Side effects of RT can be divided into acute, early-delayed, and late complications. An acute encephalopathy characterized by headache, nausea, drowsiness, fever, and sometimes worsening of neurological signs can occur within 2 weeks of RT onset [63]. Early-delayed complications (2 weeks to 3–4 months after the completion of radiotherapy) include the "somnolence syndrome" which is characterized by hypersomnia, drowsiness, and irritability [63–65]. Radionecrosis, cognitive dysfunction, and leukoencephalopathy are the main delayed complications of brain irradiation [63]. A survey on cognitive deficits in progression free survivors of low grade glioma failed to confirm a generally assumed relationship between radiotherapy and cognitive deficits [66]. Radiation-induced, progressive endocrine dysfunction of hypothalamic origin has been reported [63].

Cost Expensive.

Pharmacologic treatment: chemotherapy

- Following surgery, newly diagnosed AA is sometimes treated with concurrent RT/TMZ and adjuvant TMZ as per the standard regimen for GB [67], (class IV). Although, it is unknown whether the survival benefit achieved with radiochemotherapy in GB can and should be extrapolated to AA; randomized prospective studies are lacking [32]. Further data regarding the use of chemoradiotherapy will be obtained from EORTC 26053-22054 (CATNON Intergroup Trial), an ongoing, prospective, randomized phase III study of RT with or without concurrent and/or adjuvant TMZ in patients with non-1p/19q deleted anaplastic glioma.
- A meta-analysis of MG patients treated with nitrosurea-based therapy (lomustine or carmustine) suggested a survival benefit with chemotherapy [68], (class II).
- A phase III study randomized newly diagnosed MG patients to (A) conventional RT; (B) procarbazine, lomustine, vincristine (PCV); or (C) TMZ [32]. At occurrence of unacceptable treatment toxicity or disease progression, patients in arm (A) were treated with PCV or TMZ (1:1 random assignment), whereas patients in (B) or (C) received radiotherapy. The primary endpoint was time to treatment failure (TTF) defined as progression after radiotherapy and one

chemotherapy in either sequence. Median TTF was similar for all arms. In the AA subgroup, Progression-free survival (PFS) was 10.8 months with RT and 18.2 months with chemotherapy suggesting a role for first line chemotherapy (class II).

- Pseudoprogression is a subacute (usually within 4 months of RT completion), treatment-related reaction with or without clinical deterioration and MRI changes suggestive of tumor progression. It is observed in 20 %–40 % of MG, particularly in patients treated with RT and concurrent TMZ compared with RT alone [69, 70]. Despite the clinical or radiological suggestion of tumor progression, patients recover or stabilize without additional treatment. Pseudoprogression appears to be more common in tumors with MGMT promoter methylation [71], Pseudoprogression is not easily differentiated from tumor progression by anatomic or advanced physiologic imaging. Recognition of this phenomenon is important to reduce inappropriate changes in therapy. It is recommended that patients with clinically asymptomatic progressive lesions on MRI within the first 3 months after TMZ chemoradiotherapy should continue with adjuvant TMZ. Symptomatic patients within this timeframe should be considered for a repeat surgical resection; corticosteroids or bevacizumab are options if surgery is contraindicated (class IV).

TMZ

Standard dosage	75 mg/m^2 by mouth daily during RT and 150–200 mg/m^2 on a 5/28 day schedule for 6 months following radiotherapy.
Contraindications	Patients who have a history of hypersensitivity to TMZ or inadequate bone marrow reserve.
Main drug interactions	Valproic acid decreases TMZ clearance by about 5 %. There is no interaction with cytochrome p450 inducers.
Main side effects	The most common side effects include nausea/vomiting, constipation, and fatigue. Grade 3–4 hematologic events (thrombocytopenia or neutropenia) occur in approximately 19 %.
Special points	Caution should be exercised in patients with hepatic or renal impairment.
Cost	Expensive.

Lomustine and carmustine

Standard dosage	Lomustine (110 mg/m^2 by mouth) and carmustine (150–200 mg/m^2 intravenously) on day 1 of a 42 day treatment cycle.
Contraindications	Hypersensitivity to the drug or inadequate bone marrow reserve.
Main drug interactions	No significant interactions with drugs frequently used in neuro-oncology.
Main side effects	Nausea, vomiting, and myelosuppression (usually occurs 4 to 6 weeks after drug administration); myelosuppression may be cumulative. The occurrence of acute leukemia and bone marrow dysplasia has been reported in patients on long term therapy. Pulmonary infiltrates or fibrosis has been reported

rarely after an interval of 6 months or longer from the start of therapy with cumulative doses greater than 1100 mg/m^2.

Special points Baseline pulmonary function studies should be conducted along with pulmonary function tests during treatment to assess for risk of developing pulmonary fibrosis.

Cost Expensive.

Procarbazine

Standard dosage 60 mg/m^2 by mouth on days 8–21 of a 42 day treatment cycle.

Contraindications Hypersensitivity to procarbazine or inadequate bone marrow reserve.

Main drug interactions Ethyl alcohol should not be used since there may be a disulfiram-like reaction. Because procarbazine exhibits some monamine oxidase inhibitory (MAOI) activities, sympathomimetic drugs, and tricyclic antidepressants should be avoided.

Main side effects Leukopenia, anemia, thrombocytopenia, nausea, and vomiting.

Special points A low-tyramine diet is recommended due to the MAOI activity of procarbazine.

Cost Expensive.

Vincristine

Standard dosage 1.4 mg/m^2 intravenously (maximum dose, 2 mg) on days 8 and 29 of a 42 day cycle.

Contraindications Patients with Charcot-Marie-tooth syndrome should not receive vincristine.

Main drug interactions Cytochrome p450 inducers may alter the metabolism of vincristine.

Main side effects Hair loss, leukopenia, constipation, neuritic pain, autonomic neuropathy (abdominal pain, constipation, and ileus) and peripheral neuropathy.

Special points All patients receiving vincristine should follow a prophylactic bowel regimen of stool softeners and laxatives.

Cost Expensive.

Treatment in the elderly

- There is a perception that elderly (age >70 years) patients have more difficulty tolerating standard radiotherapy than younger patients.
- Recommended treatment options for elderly patients include standard RT or RT/TMZ (for fit, otherwise healthy elderly patients), accelerated hypofractionated radiotherapy (34–40 Gy in10–15 fractions), and primary TMZ chemotherapy with deferred RT (class IV).
- The NOA-08 trial randomized 373 patients, age >65 years, with AA or GB to standard postsurgical RT (54–60 Gy) vs TMZ (100 mg/m^2/day, 1-week-on/ 1-week-off) [15]. The TMZ arm had a similar outcome to RT suggesting that TMZ alone, particularly in those with a

methylated MGMT promoter gene, is an option for newly diagnosed, elderly AA patients [72••] (class II).

Treatment at recurrence/progression

- For tumors that progress following initial therapy, treatment options are limited.
- Re-resection can be helpful in selected patients, particularly those symptomatic from tumor mass effect and with tumors in non-eloquent brain. Although surgery may improve performance, the benefit with respect to survival has not been evaluated (class IV).
- TMZ demonstrated efficacy in a multi-center, phase II study AA initially treated with RT alone [73], (class III). The study demonstrated 6-month progression free survival (PFS-6) of 46 %, objective radiologic response rate of 35 % and OS of 13.6 months [73].
- Continuous dose-dense TMZ (50 mg/m^2/day) is an option for recurrent AA, particularly those with early progression (before completion of 6 cycles of adjuvant therapy) and in previous responders (those who progressed more than 2 months after completing adjuvant therapy) [74•], (class III). The hypothesis is that protracted TMZ dosing overcomes drug resistance by reducing intra-tumoral MGMT activity and provides an anti-angiogenic effect (limit endothelial cell recovery, inhibit the activity of circulating endothelial precursors, and up-regulate thrombospondin-1). In the study by Perry et al. PFS-6, 1-year OS, and radiographic response rate were 35.7 %, 60.7 %, and 15.4 %, respectively [74•]. It remains uncertain whether metronomic TMZ is more effective than re-challenge with standard dose TMZ in previous responders.
- The combination of bevacizumab and irinotecan was evaluated in patients with AA (n=25/33) and anaplastic oligodendroglioma (n=8/33) in a phase 2 study [75], (class III). The PFS-6, 6-month OS, and radiologic response rate were 55 %, 79 %, and 61 %, respectively, indicating that bevacizumab may have similar activity to that seen in GB. Kreisl et al. conducted a study of single agent bevacizumab in patients with recurrent MG (68 % were AA) [76•]. Median OS was 12 months. Median PFS was 2.93 months and PFS-6 (the primary endpoint) was 20.9 %. Forty-three percent of patients achieved a radiographic response. Despite the low PFS-6, patients experienced a significant clinical benefit; 67 % on corticosteroids at study onset were able to decrease the dose by an average reduction of 71 % (Class III). Forty-eight percent of patients had improved neurological symptoms with treatment.
- Re-irradiation was found to be safe and have palliative benefit in 2 single institution retrospective studies; however both suffer from their retrospective nature and likely selection bias [77, 78],

(Class IV). Large prospective studies demonstrating benefit are lacking, although the Radiation Therapy Oncology Group (RTOG) is conducting a phase II trial of concurrent bevacizumab and re-irradiation vs bevacizumab alone for recurrent GB (RTOG 1205).

- Other options at recurrence include treatment with single-agent carmustine, lomustine, or PCV (Class IV).
- Given the modest efficacy and need to define new AA treatments, enrollment on a clinical trial is encouraged at recurrence in eligible patients.

Bevacizumab

Standard dosage	10 mg/kg intravenous every weeks.
Contraindications	Hypersensitivity to bevacizumab or intracranial or systemic hemorrhage.
Main drug interactions	None.
Main side effects	Hypertension, epistaxis, proteinuria. Rare but serious side effects include infusion reaction, intracranial or systemic hemorrhage, VTE, wound dehiscence and healing impairment, and GI perforation.
Cost	Very expensive.

Irinotecan

Standard dosage	125 mg/m^2 intravenous every 2 weeks.
Contraindications	Hypersensitivity to irinotecan.
Main drug interactions	Metabolism of irinotecan is affected by cytochrome p450 inducing drugs.
Main side effects	Diarrhea, myelosuppression and nausea.
Cost	Expensive.

Emerging therapies

- Despite initial optimism, studies investigating agents that target the molecular pathology of MG have been overwhelmingly disappointing [79•]. Identifying subsets of AA with apparent oncogene addiction may permit improved efficacy of available targeted therapies. In addition, the use of correlative studies, that utilize post-treatment surgical specimens to determine if the targeted agent of interest enters the tumor and affects the targeted signaling pathway, is encouraged.
- Other therapeutic strategies under active investigation include immunotherapies, antiangiogenic agents, and viral gene therapies [79•].
- Since IDH mutations are highly prevalent and specific in AA and enzymatic defects are attractive candidates for therapeutic intervention, IDH-related therapy may play a novel role in the future treatment of AA [33•, 80]. However, the oncogenic mechanism associated

with IDH mutations is yet to be determined and currently no therapy is available that specifically targets IDH mutations.

Conflict of Interest

Sean A. Grimm has served on an advisory board and received grant support from Genentech.

Thomas J. Pfiffner declares that he has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

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- •• Of major importance

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