



Newly Diagnosed Glioblastoma in Elderly Patients

Carlen A. Yuen¹ · Marissa Barbaro^{1,2} · Aya Haggiagi^{1,3}

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Abstract

Purpose of Review Elderly patients with newly diagnosed glioblastoma (eGBM) carry a worse prognosis compared with their younger counterparts. eGBM garners special attention due to the unique challenges, including increased treatment-associated toxicity, less relative benefit from aggressive therapy, medical comorbidities, and immunosuppression. The pivotal GBM trials excluded patients > 70 years old and the optimal treatment approach remains unsettled for eGBM. In this review, we analyze the historical evidence-based data for treating eGBM and discuss the future direction for managing this vulnerable population.

Recent Findings Treatment for eGBM continues to evolve. Therapy choice is guided by performance status and presence of O6-methylguanine-DNA-methyltransferase (*MGMT*) promoter methylation. For eGBM with good performance status, combinatorial hypofractionated radiation therapy (hRT) and temozolomide should be recommended. For those with poor performance status, further stratification based on *MGMT* promoter methylation test result is recommended. Single-agent temozolomide is a viable treatment option for *MGMT* methylated tumors (m*MGMT*); in particular, those classified with receptor tyrosine kinase II methylation. hRT alone can be considered in *MGMT* unmethylated (u*MGMT*) eGBM patients. As precision oncology continues to advance, effective targeted and immunotherapy may emerge as new treatment options for eGBM.

Summary Management of elderly patients with newly diagnosed GBM carries a unique set of challenges. Progress has been made in defining the optimal therapeutic approach for these patients, but many questions remain to be answered.

Keywords Elderly · Glioblastoma · Hypofractionated radiation therapy · Temozolomide · Bevacizumab · Tumor-treating fields

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✉ Aya Haggiagi
amh2237@cumc.columbia.edu

Carlen A. Yuen
cay2115@cumc.columbia.edu

Marissa Barbaro
marissa.barbaro@nyulangone.org

¹ Division of Neuro-Oncology, Department of Neurology, Columbia University Vagelos College of Physicians and Surgeons, New York-Presbyterian Hospital, 710 W 168th St, 9th Floor, New York, NY 10032, USA

² Present Address: Perlmutter Cancer Center at NYU Langone Hematology Oncology Associates – Mineola, NYU Long Island School of Medicine, NYU Langone Health, Mineola, NY, USA

³ Herbert Irving Comprehensive Cancer Center, Columbia University Vagelos College of Physicians and Surgeons, New York-Presbyterian Hospital, New York, NY, USA

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor with an age-adjusted incidence that increases with age. According to the most recent Central Brain Tumor Registry of the United States (CBTRUS) statistical report, the highest incidence of GBM occurs among patients > 75 years of age [1]. Despite representing the age group with the highest incidence of GBM, elderly patients with newly diagnosed GBM (nd eGBM) have been underrepresented in prospective studies. Both the landmark Stupp et al. trial [2] and the most commonly utilized prognostic schema for malignant gliomas excluded patients > 70 years of age [3]. This unmet need was later recognized, and clinical trials were subsequently conducted specifically for eGBM. Though progress has been made, many questions are unanswered, including the age cut-off for defining “elderly” and equally as important, the optimal treatment for

eGBM. Age has been the most significant predictor of treatment decision-making, which is driven by frailty, increased comorbidities, and increased risk of toxicity [4–7]. Due to these unique challenges, eGBM patients have been treated with less aggressive therapy [7–12], which may have altered their outcome. In this review, we analyze the current treatment approaches for nd eGBM and explore the questions that remain open for future investigation.

Molecular Signature of GBM in Older Adults

The poorer prognosis observed in eGBM has been attributed in part to the comorbidities that accompany advancing age. However, further disparities between older and younger patients can be due to differences in the intrinsic properties of eGBM, including the tumors' molecular characteristics and mutations. The proneural GBM subtype is associated with improved prognosis [13], but is an uncommon entity in eGBM [14]. eGBM lack the isocitrate dehydrogenase (*IDH*) mutations [15] that confer survival advantage [16, 17] and are rarely found in gliomas of older patients [17–19]. Only 3 of 126 gliomas of older patients in the Neurooncology Working Group (NOA) of the German Cancer Society Study 8 (NOA-08) [20] and 2 of 299 gliomas of older patients in the Nordic trials were found to have an *IDH R132H* mutation [21]. Additionally, in a cost-effectiveness study conducted by DeWitt et al., only 2 of 1023 GBM \geq 55 years of age were found to have a non-canonical *IDH* mutation, suggesting that sequencing testing based on age can be considered [22]. Though the authors found low value in screening for a non-canonical *IDH* mutation in older GBM patients, the authors also recognized that molecular testing in older patients can provide meaningful information [22].

The O6-methylguanine–DNA methyltransferase (*MGMT*) gene encodes an enzyme involved in DNA repair [20] and has a significant prognostic impact in GBM [23]. Hypermethylation of the *MGMT* gene promoter (*mMGMT*) silences the gene [23] and is found in up to 45 to 57.8% of eGBM [24, 25]. The Nordic trial showed survival advantage for *mMGMT* tumors compared to *uMGMT* with an increase in OS of 9.7 months vs. 6.8 months for eGBM [21]. The NOA-08 trial showed similar findings with improved OS of 11.9 months vs. 8.2 months in *mMGMT* compared to *uMGMT* in eGBM [20]. Taken together, *MGMT* is a strong independent prognostic biomarker for eGBM patients [23, 26]. Nevertheless, it is important to note that data from NOA-08 trial were immature at initial publication with median OS documented for only 61.1% of patients [20].

mMGMT also plays a strong predictive role as a marker of response to alkylating therapy. *mMGMT* abrogates the effects of alkylating chemotherapy by rendering the cancer cell unable to repair induced DNA damage [23].

Accordingly, *mMGMT* status is correlative with temozolomide (TMZ) sensitivity [20, 21, 23, 26].

More recent studies exploring genomic alterations associated with the eGBM molecular underpinnings [27] have found that tumor protein (*TP*)53 mutations [28], somatic copy number alterations, cyclin-dependent kinase (*CDK*)4 amplification [29], *CDKN2A/p16* alterations [28], telomerase reverse transcriptase (*TERT*) promoter mutations [30], epidermal growth factor receptor (*EGFR*) alterations, chromosome 7 gain, 9p loss and 13 q loss [31] are negative prognostic factors for eGBM. *TERT* gain-of-function promoter mutations occur more commonly in elderly gliomas [29, 32]. In 2018, Sasaki *et al.* performed a retrospective study on 140 elderly gliomas and found that presence of *TERT* promoter mutation was associated with decreased survival [33]. *TERT* promoter mutations have also been newly identified as molecular criteria for aggressive behavior in the new 2021 WHO Classification of Tumors of the Central Nervous System, in addition to and *EGFR* amplification [15, 34]. While theoretically these unfavorable eGBM specific molecular alterations can be capitalized upon, no targeted therapy has been proven to be beneficial in eGBM to date. In contrast to these eGBM negative prognostic factors, other studies have found favorable prognostic markers in eGBM, including anti-vascular endothelial growth factor (VEGF) [27]. Alpha thalassemia X-linked intellectual disability syndrome gene (*ATRX*) alterations are also associated with favorable prognosis, but are uncommon in older GBM patients [35]. Further studies to evaluate the impact of molecular biomarkers on the prognosis of eGBM will lead to better understanding of the basis for age-specific outcome differences and development of novel therapeutic targets.

Surgery

eGBM inherently carry a worse prognosis compared to their younger counterparts [8, 18, 36], which has historically hindered the decision to operate on these patients [12, 37]. While post-operative seizures and delirium in eGBM patients were reported in one study [6], other studies found no increase in surgical complications with extensive resection compared to biopsy in eGBM [38–41]. Moreover, extent of resection improves OS in eGBM [20, 21, 38, 42–44], and older age alone should not be exclusionary for aggressive surgery [45]. A retrospective study conducted by Chaichana *et al.* found that extensive resection improved OS compared to biopsy in 40 eGBM older than > 65 years and even in patients > 70 years [38]. Another long-term retrospective study by Heiland *et al.* between 2008 and 2017 of 341 eGBM > 65 years showed that the longest median OS was associated with patients who underwent gross total resection, compared to partial resection or biopsy (10.8 months,

8.1 months, and 3.0 months, respectively, $p \leq 0.001$) [46]. The 2020 guidelines for nd GBM recommend GTR for eGBM based on level III evidence [47]. In summary, current evidence is convincing for survival benefit with maximal safe surgical resection in this population [37, 39, 48], and older age alone should not preclude eGBM from aggressive surgery.

Current Post-Operative Therapeutic Strategies

While concurrent standard radiation therapy (sRT) consisting of 60Gy in 30 fractions with daily TMZ followed by at least 6-months of adjuvant TMZ is the standard of care for younger patients with nd GBM, the optimal treatment for “elderly” patients remains unsettled as most randomized clinical trials (RCTs) until recently have excluded patients > 70 years of age [2]. Historically, there has been interest in “de-intensifying” therapy for eGBM. This was driven by a need to balance the benefit of post-operative standard combination chemoradiation therapy with the risk of side effects in patients > 65 years of age and in particular, those > 70 years of age, with a low Karnofsky performance status (KPS) and multiple medical comorbidities. In the Stupp et al. trial, less apparent survival benefit was observed in patients > 60 years of age (median survival 11.8 months with RT alone vs 10.9 months with combination therapy) [49]. However, the numbers were too small to draw firm conclusions. Notably to date, standard combination therapy has not been evaluated

in RCTs for patients >70 years of age. Instead, radiation or TMZ monotherapy became a common alternative treatment strategy, particularly after the results of two key RCTs for this patient population were published in 2012 (NOA-08 and the Nordic trials), which compared single modality therapies. Prospective studies specifically designed for eGBM are summarized in Table 1.

Radiation Therapy

sRT delivered over 6 weeks provides a significant survival advantage over supportive care in eGBM [50] based on evidence from the Association des Neuro-Oncologues d’Expression Française (ANOCEF) trial (NCT00430911) that studied eGBM > 70 years of age treated with biopsy or resection followed by sRT (50 Gy in 1.8 fractions) [50]. The authors also found that sRT had no adverse impact on cognition or quality of life (QoL) [50]. Conversely, other studies show poor adherence to a 6-week RT treatment schedule, with 19–26% of eGBM unable to tolerate the standard treatment time burden [21, 51, 52]. Hypofractionated RT (hRT) offers the benefit of a less intensive treatment schedule for eGBM. In 2004, Roa et al. investigated an abbreviated RT course (40 Gy in 15 fractions over 3 weeks) compared to the sRT course (60 Gy delivered in 30 fractions over 6 weeks). There was no difference in overall survival (OS) or QoL when hRT comparing to sRT, suggesting that an abbreviated RT course may be beneficial for eGBM with poor performance status and an expected short-term survival [51]. In 2012, the Nordic trial randomized 291 patients > 60 years

Table 1 Elderly glioblastoma patient trials

Study	Age	Patients	Treatment	Dosing regimen	Median OS (months)
Nordic Malmstrom et al. [20]	≥ 60	291	TMZ	5/28 days	8.3
			hRT	34 Gy	7.5
			RT	60 Gy	6.0
	> 70	123	TMZ	5/28 days	9.0
			RT	34 Gy	7.0
			RT	60 Gy	5.2
NOA-08 Wick et al. [19]	> 65	373	RT	60 Gy	9.6
CCTG/EORTC 26062 Perry et al. [64]	> 65	562	TMZ	7 days on, 7 days off	8.6
			RT+TMZ	60 Gy	5.3
ANOCEF trial Keime-Guibert et al. [50]	≥ 70	85	RT+TMZ	40 Gy	9.3
			RT	50 Gy	6.7
			Supportive care		3.9

NOA Neurooncology Working Group; Canadian Cancer Trials Group (CCTG); EORTC European Organisation for Research and Treatment of Cancer (EORTC); ANOCEF The Association des Neuro-Oncologues d’Expression Française; TMZ temozolomide; hRT hypofractionated radiation therapy

of age with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 to sRT (60Gy in 30 fractions), hRT (34Gy in 10 fractions), or TMZ. OS was longer in patients > 70 years of age who were treated with TMZ or hRT compared with those who received sRT [21]. An even more abbreviated course of 25 Gy in 5 fractions was found to be non-inferior to the 40 Gy course, but its use is controversial [53–55]. Moreover, in 2019, the coronavirus disease 2019 (COVID-19) pandemic compelled organizations to expeditiously update the existing treatment recommendations for immunosuppressed patients, including elderly patients. Elderly patients infected with COVID-19 experience worse outcome, thereby supporting rationale for a shorter RT treatment schedule to mitigate exposure risk to the virus [56•]. In summary, RT for eGBM improves OS compared to best supportive care without compromising QoL or cognition and hRT should be considered in patients > 65–70 years of age. Withholding RT can be justified in a subset of eGBM with *mMGMT* tumors and poor KPS. This is further discussed in the monotherapy section.

Combination Chemoradiation Therapy with TMZ

A recent retrospective study of all GBM patients from the US National Cancer Database between 2005 and 2016 showed that older age negatively impacts the likelihood of receiving combination chemoradiation [7]. Other negative impact factors associated with older age include Medicaid or no insurance, lower income bracket, and existing comorbidities [7]. Growing evidence supports the use of aggressive treatment with maximal safe resection, sRT, and chemotherapy in select eGBM with good functional status [7, 12, 36, 57•, 58], but has not been prospectively studied. In 2008, Minniti et al. conducted a single-arm prospective study of 32 eGBM age > 70 years using combination therapy with sRT and reported median OS of 10.6 months [59]. In 2009, a long-term 5-year follow-up subgroup analyses of the European Organisation for Research and Treatment of Cancer (EORTC) 26981-National Cancer Institute of Canada (NCIC) CE.3 trial found that combination chemoradiation conferred a survival advantage compared to RT alone [49]. However, this benefit diminished with increasing age [49, 60], with less overall benefit in patients > 60 years of age compared to RT alone (10.9 months vs. 11.8 months) [49]. At 2-year follow-up, the survival benefit with combined therapy was 21.8% vs 5.7%, but the benefit was marginal at 5-year follow-up (6.6 vs. 0%) [49]. In a large retrospective review conducted by Pretanvil et al. of 2670 eGBM >70 years diagnosed between 2005 and 2010, combination chemoradiation resulted in the longer OS compared to surgery and RT or surgery alone in eGBM (8 months, 5 months, and 3 months, respectively) [12]. In a recent 2020 meta-analysis of treatment for nd eGBM, Hanna et al. found strong evidence

for increased OS with combined chemoradiation compared to RT alone [57•].

In contrast, other studies found no survival benefit with combination therapy in eGBM [61]. In a 2012 10-year retrospective study, Cao et al. reported decreased survival in eGBM with combined chemoradiation compared to hRT followed by salvage TMZ (6.9 months vs. 13.3 months) [61]. Minniti et al. conducted a retrospective study of 127 eGBM comparing hRT to sRT in combination therapy [62]. Results of this study showed similar median OS (6.7 months vs. 5.6 months, respectively) [62], but significantly increased neurotoxicities and poorer performance status in the patients who received sRT [62]. Additional studies report increased toxicity from combination therapy with sRT [24, 57•, 63], with 42% of elderly patients developing neurocognitive decline [63] and Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicities compared to treatment with RT alone [24]. In 2017, the Canadian Cancer Trials Group (CCTG)/EORTC 26062 trial found that combinatorial hRT and TMZ improves survival over hRT alone [64] and can be considered for eGBM with good performance status.

Monotherapy with RT or TMZ

eGBM patients with poor KPS may not be able to tolerate combined chemoradiation. For these patients, monotherapy with TMZ or RT may be warranted. Evidence derived from multiple prospective studies advocate for the tailoring of monotherapy based on *MGMT* promoter methylation status [26, 54, 65–68]. The 2011 ANOCEF trial found that TMZ monotherapy in patients > 70 years of age was well tolerated and resulted in improved median OS compared to supportive care alone (25 weeks vs. 12–16 weeks), with greater survival benefit in *mMGMT* eGBM compared to *uMGMT* eGBM [69]. Subgroup analyses from the 2012 Nordic and NOA-08 trials also argue for the use of TMZ monotherapy in *mMGMT* eGBM [20, 21]. The Nordic trial randomized patients to three different arms of sRT, hRT, or TMZ (200mg/m² for 5 consecutive days over 28-day cycles) [21]. Results showed that both TMZ alone and hRT alone were superior to sRT for eGBM > 70 years of age (TMZ vs sRT HR = 0.35 (0.21–0.56), $p < 0.0001$) [21]. The NOA-08 non-inferiority trial (NCT01502241) randomized 371 patients ≥ 65 years of age with GBM ($n = 331$) or anaplastic astrocytoma ($n = 40$) and KPS of > 60 to dose-dense (DD) TMZ (100mg/m², 1 week on/1 week off) or sRT (30 fractions of 1.8 to 2.0 Gy delivered over 6–7 weeks to a total dose 60 Gy) [20]. DD adjuvant TMZ was found to be non-inferior to sRT (OS 8.6 months vs. 9.6 months) [20]. Taken together, results from these studies suggest that single-agent TMZ is a reasonable alternative therapy for *mMGMT* eGBM with poor KPS [69] and significant medical comorbidities. More recently, methylation profiling has garnered attention

for more accurate classification of gliomas as shown in the intriguing findings from the newly published long-term follow-up data of the NOA-08 trial; the *mMGMT* receptor tyrosine kinase (RTK) II methylation class of GBM showed the greatest benefit from TMZ [70••]. The authors also concluded that RTK I and mesenchymal methylation classes did not derive benefit from TMZ and alternative therapies should be considered for these patients [70••]. However, attention should be drawn to the lack of consistency in the dosing and duration of TMZ among these studies. Furthermore, survival outcomes on single-agent TMZ vs. combined chemoradiation have not been studied.

For *uMGMT* eGBM, RT monotherapy is favored over single-agent TMZ [20, 54, 71] and is an acceptable alternative to combination chemoradiation [20]. The 2016 Project of Emilia Romagna Region on Neuro-Oncology (PERNO) prospective study included 76 patients > 70 years of age and found less survival benefit with *uMGMT* compared to *mMGMT* tumors treated with RT/TMZ (8.8 months vs. 17.2 months) [72]. The CCTG/EORTC 26062 trial showed similar findings of decreased survival benefit with the addition of TMZ in *uMGMT* compared to *mMGMT* eGBM [64]. Recent literature provides justification to withhold TMZ for eGBM with *uMGMT* tumors during the COVID-19 pandemic [73].

Notably, though *MGMT* promoter methylation status is essential for treatment decision-making in eGBM, consensus is lacking on the optimal testing method [71], threshold or cut-off values, and identification of the specific CpG sites that are required to be methylated to induce the transcriptional silencing [68, 71]. Additionally, methylation-specific assays can be qualitative or quantitative and can differ in their analyses of distinct CpG sites [68], which can lead to variable results, particularly with limited biopsy tissue samples. We suggest confirming *MGMT* promoter methylation test result in eGBM by at least two independent assays when methylation is not detected.

Bevacizumab (BEV)

BEV, a VEGF monoclonal antibody, was studied in a phase 2 trial in combination with RT in GBMs [74]. The Phase 2 Avastin Plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) trial investigated survival benefit with the addition of BEV to hRT in patients > 65 years of age with nd eGBM [75]. Findings from this study recapitulated prior trial results of the addition of BEV for progressive GBMs [76–78], improving PFS, but not OS (PFS-3 of 7.6 vs. 4.8 months, $p = 0.003$) [79]. Early data from a phase 2 clinical trial investigating the use of BEV in combination with TMZ for eGBM (NCT01149850) [80] showed promising results with possible survival benefit and good tolerability [81]. However, a recent 2020 meta-analysis on nd eGBM found low evidence for BEV use in this patient population

with higher risk of adverse events [57•]. The neuropsychiatric adverse events and cognitive decline observed in the eGBM patients who received BEV [75] were consistent with the decline in QoL and inferior cognitive functioning reported in the RTOG 0825 trial [76].

Tumor-Treating Fields (TTF)

TTF deliver low-intensity alternating electric fields and anti-mitotic activity through a portable medical device [82, 83]. TTF are FDA approved for nd GBM based on results from the multicenter, prospective, randomized phase 3 EF-14 trial [83]. Combination therapy followed by TTF improves survival by nearly 5 months compared to TMZ alone (20.5 months vs. 15.6 months) [83]. A post-hoc analysis of the 134 eGBM ≥ 65 years of age in the EF-14 study showed improved median OS of 17.4 months vs. 13.7 months with the addition of TTF to TMZ compared to TMZ alone [82]. Another post-hoc analysis of the EF-14 trial showed that the greatest survival advantage was associated with eGBM > 65 years of age and the addition of TTF resulted in a gain of 1.75 incremental life years compared to TMZ alone with good tolerability [84]. Recently, a 2020 large retrospective study of 11,029 patients treated with TTF (26% of whom were elderly) found that eGBM experienced the lowest rate of electric and heat sensations, headache, and discomfort [85].

Future Directions

eGBM patients are undoubtedly a special patient population with a unique set of therapeutic challenges. Recognition of the higher risk for neurocognitive toxicities in eGBM is imperative, but geriatric assessments (GAs) are lacking in eGBM clinical trials [86]. The comprehensive geriatric assessment (CGA) is in use for elderly patients with cancer, but not GBM [87]. A recent 2019 retrospective study showed that the CGA is prognostic for eGBM and may potentially inform which patients will benefit from combined chemoradiation [87]. In 2020, the first prospective study evaluating the utility of neurologic-based GAs was conducted in the geriatric assessment for OLDER patients with Glioblastoma within Neuro-oncology clinics (GOLDEN) study and found that GAs provide prognostic value and are feasible to perform [88].

fNovel therapeutic approaches are needed in eGBM as prognosis remains dismal. Immunotherapy has revolutionized cancer therapy, but has yet to show survival benefit in GBM or eGBM [37]. The Nivolumab and Temozolomide Versus Temozolomide Alone in Newly Diagnosed Elderly Patients with GBM (NUTMEG) trial is phase 2 study investigating the effects of combinatorial adjuvant nivolumab and

TMZ vs. TMZ alone in nd eGBM (NCT04195139) [89]. The impact of immunosenescence in eGBM [90], tumoral heterogeneity, and tumor microenvironment immunosuppression [91] are challenges that are paramount to overcome in order to increase responsiveness to immunotherapy [90]. Moreover, it remains unclear which subgroups of GBM patients may benefit from immunotherapy. High tumor mutational burden (TMB) in comparison to intermediate or low mutational burden may be associated with increased sensitivity to anti-programmed death-ligand 1 (PD-L1) inhibitors in other cancers [92], but immune checkpoint blockade has not shown benefit in GBM [93, 94]. However, isolated cases in non-elderly GBM patients have shown success [95, 96]. Advances in molecular profiling may identify biomarkers of checkpoint sensitivity and inform which subgroups of eGBM may benefit from immunotherapy.

Targeted therapy driven by enhanced understanding of the molecular biology of GBM is an active area of research with many new innovative clinical trial designs utilizing new data; enrollment of eGBM patients on these trials should be encouraged. For example, an ongoing phase 1/2 *TERT* derived vaccine trial (NCT04280848) investigating telomerase-targeting GBM peptides is currently underway, and patients up to 75 years of age are eligible [97]. Similarly, CDK inhibitors may play a role in eGBM. Preliminary results from a phase 2/3 trial studying abemaciclib in GBM showed increased PFS compared to control (NCT02977780 “Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGHT)”) trial [98–100].

Conclusion

Elderly patients with newly diagnosed GBMs warrant special attention in their treatment approach. High functioning eGBM patients should be considered for combined chemoradiation therapy. Those with poor functioning can be stratified for monotherapy based on *MGMT* promoter methylation status. For *mMGMT* tumors, single-agent TMZ can be considered, while hypofractionated RT alone may be sufficient for *uMGMT* tumors. Despite treatment (combination or monotherapy), prognosis of eGBM remains grim, and better understanding of the molecular signature of these tumors is of paramount importance as it will help elucidate the causes for age-specific different outcome and open the door to development of new novel therapies.

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- Of importance
- Of major importance

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