Glioblastoma recurrence case series

2024

In a retrospective cohort study, Zhang et al. set out to examine the relative effects of bevacizumab and Gamma Knife radiosurgery on progression-free survival (PFS) and overall survival (OS) in patients with GBM at first recurrence.

They conducted a retrospective review of all patients with rGBM who underwent treatment with bevacizumab and/or Gamma Knife radiosurgery at Roswell Park Comprehensive Cancer Center between 2012 and 2022. Mean PFS and OS were determined for each of our three treatment groups: Bevacizumab Only, Bevacizumab Plus Gamma Knife, and Gamma Knife Only.

Patients in the combined treatment group demonstrated longer post-recurrence median PFS (7.7 months) and median OS (11.5 months) compared to glioblastoma patients previously reported in the literature and showed improvements in total PFS (p=0.015), total OS (p=0.0050), post-recurrence PFS (p=0.018), and post-recurrence OS (p=0.0082) compared to patients who received either bevacizumab or Gamma Knife as monotherapy.

This study demonstrates that the combined use of bevacizumab with concurrent stereotactic radiosurgery can improve survival in patients with rGBM [1].

2022

Park et al. retrospectively collected the data of r/rGBM patients treated with the combination of bevacizumab and irinotecan (BEV+IRI) as their salvage therapy from July 2013 and December 2021 in Konkuk Medical Center of Korea. Patients with available results from molecular diagnostic tests were eligible, and markers of interest were examined including the presence of MGMT methylation, IDH1/2 mutation, or 1p/19q co-deletion. Efficacy of BEV+IRI and its potential biomarker was explored.

Results: Among 21 patients, 38.1% demonstrated Eastern Cooperative Oncology Group Performance Status ≥3. The majority (71.4%) received BEV+IRI as their second-line chemotherapies, and the median dose was 5 (range=1-25). Objective response rate (ORR) was 33.3% and disease-control rate (DCR) was 85.7%. Irrespective of objective response, early clinical response was achieved in 14(66.7%) patients. During the median follow-up of 16.4 months for survivors, median progression-free survival (PFS) and overall survival (OS) were 3.6 and 6.8 months, respectively. ECOG PS≥3 and TP53 loss were independent predictors of an unfavorable OS, while prompt clinical improvement could predict favorable OS. Any molecular aberration was associated with OS or PFS in the study.

Salvage BEV+IRI treatment in r/rGBM conferred comparable clinical benefit. ECOG PS ≥3, TP53 loss, and lack of prompt clinical improvement after the treatment were significantly associated with an unfavorable OS [2]

2021

Montemurro et al. conducted a retrospective cohort study of 63 patients (mean age 59.2 years) surgically treated at least two times for recurrent Glioblastoma between 2006 and 2020.

Median OS and progression-free survival (PFS) were 22 months (range 2-168 months) and 10 months (range 1-96 months), respectively. The OS following gross-total resection (GTR) at recurrence for patients with initial GTR (GTR/GTR) was significantly increased (42.6 months) compared with sub-total resection (STR) at reoperation after initial GTR (GTR/STR) (19 months) and with GTR at reoperation after initial STR (STR/GTR) (17 months) (p = 0.0004). Overall surgical morbidity resulted 12.7% and 11.1% at first and at second surgery, respectively. Changes in genetic profiles between first and second surgery of 1p/19q co-deletion, MGMT promoter methylation and p53 mutations occurred in 5.6%, 1.9% and 9.3% of cases, respectively. MGMT promoter methylation appeared to affect OS in univariate analysis at first (p = 0.038) and second surgery (p = 0.107), whereas p53 mutation appeared to affect OS only at second surgery (p = 0.01). In a multivariate analysis female sex (HR = 0.322, 95% CI 0.147-0.705; p = 0.005), PFS (HR = 0.959, 95% CI 0.934-0.986; p = 0.003), GTR at first and second surgery (HR = 0.195, 95% CI 0.091-0.419; p < 0.0001) and adjuvant chemotherapy at recurrence (HR = 0.407, 95% CI 0.206-0.809; p = 0.01) were associated with longer OS.

This study confirmed the role of Glioblastoma extent of resection (EOR) at first and at recurrence as a significant predictor of outcome. In addition, this study highlighted the concept of a dynamic evolution of Glioblastoma genome after initial surgical resection, supporting the need of further studies to investigate the clinical and therapeutic implications of the changes in genetic profiles after initial surgery [3)]

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47 patients with rGlioblastoma were enrolled in a prospective phase II convection-enhanced delivery of an IL4R-targeted immunotoxin (MDNA55-05, NCT02858895). Bidirectional tumor measurements were created by local sites and centrally by an independent radiologic faculty (IRF), then standard RANO, iRANO, and mRANO criteria were applied.

Results: 41 of 47 patients (mean age 56{plus minus}11.7) were evaluable for response. PFS was significantly shorter using standard RANO compared to iRANO (log-rank, P<0.0001; HR=0.3) and mRANO (P<0.0001;HR=0.3). In patients who died and had confirmed progression on standard RANO, no correlation was observed between PFS and OS (Local, P=0.47; Central, P=0.34). Using iRANO, a weak association was observed between confirmed PFS and OS via local site measurements (P=0.017), but not central measurements (P=0.18). 24 of 41 patients (59%) were censored using iRANO and because they lacked confirmation of progression 3 months after initial progression. A strong correlation was observed between mRANO PFS and OS for both local (R2 =0.66,P<0.0001) and centrally-determined reads (R2 =0.57,P=0.0007).

No correlation between radiographic PFS and OS was observed for standard RANO or iRANO, but a correlation was observed between PFS and OS using the mRANO criteria. Also, the iRANO criteria were difficult to implement due to needing to confirm progression 3 months after initial progression, censoring more than half the patients [4)].

2019

All patients with Glioblastoma recurrence between 2005 and 2015, who were discussed by the institution's multi-disciplinary team, and who either did or did not undergo reoperation, were prospectively followed up with data collected and compared. Survival and prognostic factors were analyzed using Kaplan-Meier and Cox regression methods.

312 patients (reoperated, n = 145; non-reoperated, n = 167) were analyzed. Median SSR was 10.8 months and 6.9 months in the reoperated and non-reoperated groups respectively (Log-rank test: $p = 0.02$). Median OS was 24.1 months and 20.4 months in the reoperated and non-reoperated groups, respectively (Log-rank test: $p = 0.04$). Quality of life as measured by Short Form 36 scores were 59 versus 54 at baseline and 62 versus 51 at four-month follow-up for re-operated and non-reoperated groups, respectively ($p < 0.05$). Age < 60 years, Karnofsky Performance Status (KPS) ≥ 80, recurrence ≥ 9 months from initial diagnosis, methylguanine methyltransferase (MGMT) promoter methylation, and extent of resection (EOR) > 80 %, each were significant predictors of SSR and OS. Complication rates were 5.5 % and 6.2 % following repeat resection and primary resection, respectively ($p > 0.05$).

This is the first large prospective comparative cohort study of rGlioblastoma and demonstrates that repeat resection confers a small but significant benefit in survival and quality of life over non-operative treatment. Best prognosis is associated with: younger age, KPS ≥ 80, late recurrence, MGMT promoter methylation and EOR > 80 % [5].

Adult patients with glioblastoma who initiated bevacizumab at disease progression between January 1, 2009, and May 14, 2012, were included. A Kaplan-Meier estimator was used to describe overall survival (OS), progression-free survival (PFS), and time to greater than or equal to 20% reduction in Karnofsky Performance Status (KPS). The effect of baseline demographic and clinical factors on survival was examined using a Cox proportional hazards model. Adverse event (AE) data were collected.

Seventy-four patients, with a median age of 59 years, were included in this cohort. Between bevacizumab initiation and first failure, defined as the first disease progression after bevacizumab initiation, biweekly bevacizumab and bevacizumab/irinotecan were the most frequently prescribed regimens. Median duration of bevacizumab treatment until failure was 6.4 months (range, 0.5-58.7). Median OS and PFS from bevacizumab initiation were 11.1 months (95% confidence interval [CI], 7.3-13.4) and 6.4 months (95% CI, 3.9-8.5), respectively. Median time to greater than or equal to 20% reduction in KPS was 29.3 months (95% CI, 13.8-∞). Lack of corticosteroid usage at the start of bevacizumab therapy was associated with both longer OS and PFS, with a median OS of 13.2 months (95% CI, 8.6-16.6) in patients who did not initially require corticosteroids versus 7.2 months (95% CI, 4.8-12.5) in those who did (P = 0.0382, log-rank), while median PFS values were 8.6 months (95% CI, 4.6-9.7) and 3.7 months (95% CI, 2.7-6.6), respectively (P = 0.0243, log-rank). Treatment failure occurred in 70 patients; 47 of whom received salvage therapy, and most frequently bevacizumab/carboplatin (7/47; 14.9%). Thirteen patients (18%) experienced a grade 3 AE of special interest for bevacizumab.

Treatment patterns and outcomes for patients with Glioblastoma recurrence receiving bevacizumab in a real-world setting were comparable with those reported in prospective clinical trials [6].

2018

A total of 3,963 patients with a mean age 74.7 years. 496 (12%) of the patients with Glioblastoma recurrence underwent at least one reoperation at an average of 7.2 months after the initial diagnosis. Reoperation increased survival in patients compared to those who did not have surgical resection (12 month vs. 5 months; p<.0001) (HR 0.666). Within the reoperated cohort, gross total resection improved median survival over subtotal resection (HR 0.779). Two or more reoperations upon Glioblastoma recurrence improved survival to 17 months (P = 0.002). The overall complication rate was 21.7% in the initial resection only group, versus 20.4% in the one reoperation group and 25.3% in the two reoperation group.

Though definitive conclusions cannot be made given the lack of granularity, this national database study supports gross total resection as the initial treatment of choice, followed by reoperation at the time of recurrence, if tolerated, even in elderly patients [7)]

2017

76 patients with Glioblastoma recurrence were analyzed. The overall response rate was 59.2%, including 19 patients (25.0%) with complete response and 26 patients (34.2%) with partial response. The median progression-free survival and overall survival were 5.2 months (95% confidence interval [CI], 4.6-5.8 months) and 7.8 months (95% CI, 5.8-9.8 months), respectively. Multivariate analysis identified sex and grade 3 posttreatment hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) as the only independent predictive factors for progression-free survival and overall survival. Eastern Cooperative Oncology Group performance status was also found to be independently predictive of improved overall survival.

We showed good responses using bevacizumab and the progression-free survival and overall survival were comparable with those previously reported. The adverse events of bevacizumab in our study were generally acceptable and manageable. Female sex, good performance status, and grade 3 posttreatment hypertension were suggested to be associated with survival benefits [8)].

Patients with Glioblastoma recurrence operated on between 2007 and 2014 were divided into 3 groups: >65 years with carmustine wafer (BCNU wafer) implantation, >65 years without BCNU wafer implantation, and ≤65 years with BCNU wafer implantation. We compared survival and complications.

A total of 79 patients were identified: 24 in the older BCNU group (median age 68.2 years, 33.3% with a methylated MGMT promoter), 16 in the older non-BCNU group (median age 68.6 years, 31.3% with a methylated O6 methylguanine DNA methyltransferase), and 39 in the younger BCNU group (median age 56.8 years). Survival after progression was 9.2 months in the elderly BCNU group and 7.6 months in the elderly non-BCNU group (p = 0.34); overall survival was 17.2 and 15.9 months, respectively (p = 0.35). Klein et al. found a tendency toward a higher rate of seizures and pneumonia in the older BCNU group.

BCNU wafer implantation after resection of recurrent Glioblastoma is a reasonably safe treatment in patients aged >65 years. Seizures and systemic infections may occur more frequently, but the trade-off is still favorable as survival may be influenced positively. Higher age should not be regarded as a

contraindication for BCNU wafers [9].

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66 patients with Glioblastoma recurrence, treated with bevacizumab. Patients received a baseline and 8-week follow-up MRI including 1 H/31 P MRSI (spectroscopy) on a 3T clinical scanner, until progressive disease according to Response Assessment in Neuro-Oncology (RANO) criteria occurred. Fourteen patients showed a distant or diffuse tumor recurrence (subsequent tumor) during treatment and were therefore selected for further evaluation. At the site of the subsequent tumor, an area of interest for MRSI voxel selection was retrospectively defined on radiographically unaffected baseline MRI sequences.

Before treatment, pHi in the area of interest (subsequent tumor) was significantly higher than pHi of the contralateral normal-appearing tissue (control; $P < 0.001$). It decreased at the time of best response ($P = 0.06$), followed by a significant increase at progression ($P = 0.03$; baseline mean: 7.06, median: 7.068, SD: 0.032; best response mean: 7.044, median: 7.036, SD: 0.025; progression mean: 7.08, median: 7.095, SD 0.035). Until progression, the subsequent tumor was not detectable on standard MRI sequences. The area of existing tumor responded similar, but changes were not significant (decrease $P = 0.22$; increase $P = 0.28$).

Elevated pHi in radiographically unaffected tissue at baseline might precede MRI-detectable progression in patients with Glioblastoma recurrence treated with bevacizumab [10].

2016

In a cohort of 204 patients with de novo glioblastoma, 49 (24%) received reoperation at recurrence. The median overall survival in the reoperation group was 20.1 months compared with 9.0 months in the nonreoperation group (P = .001). Reoperation was associated with longer overall survival in the total population (hazard ratio, 0.646; 95% confidence interval, 0.543-0.922; P = .016) but subject to selection bias. Subgroup analyses excluding patients unlikely to be considered for reoperation suggested a much less significant effect of reoperation on survival, which warrants further study with larger cohorts. Factors at initial surgery predictive for reoperation were younger age, smaller tumor size, initial extent of resection ≥50%, shorter inpatient stay, and maximal initial adjuvant therapy. When unfavorable patient characteristics are excluded, reoperation is not an independent predictor of survival.

Patients undergoing reoperation have favorable prognostic characteristics, which may be responsible for the survival difference observed. Tully et al., recommend that a large clinical registry be developed to better aid consistent and homogenous data collection [11].

2015

Optimal treatment of Glioblastoma recurrence (rGlioblastoma) in elderly and/or frail patients remains virtually unexplored, the best supportive care (BSC) only is routinely administered due to the fatal prognosis.

Socha et al. evaluated the impact of different treatment methods on post-progression survival (PPS) and overall survival (OS) of such patients. Data from 98 elderly and/or frail rGlioblastoma patients, treated initially with 1-week or 3-week radiotherapy (RT) within the phase III IAEA study (2010-2013),

were analyzed. KPS at relapse and salvage treatment methods were recorded. Kaplan-Meier method was used to estimate PPS and OS for different treatment modalities. Eighty-four patients experienced recurrence: 47 (56 %) received BSC, 21 (25 %)-chemotherapy (CHT), 8 (9.5 %)-surgery, 3 (3.5 %)-RT, for 5 (6 %) the data was unavailable. Median OS from randomization for all 84 patients was 35 weeks: 55 versus 30 weeks for any treatment versus BSC, $p < 0.0001$. Median PPS was 15 weeks: 23 weeks with any treatment versus 9 weeks with BSC, $p < 0.0001$. For local treatment (surgery and/or RT) median PPS was 51 versus 21 weeks for CHT, $p = 0.36$. In patients with poor KPS (≤60) at relapse median PPS was 9 weeks with BSC versus 21 weeks with any treatment, $p = 0.014$. In poor KPS patients median PPS for local treatment was 14 weeks versus 21 weeks with CHT, $p = 0.88$. An active therapeutic approach may be beneficial for selected elderly and/or frail rGlioblastoma patients. Poor KPS patients may also benefit from active treatment, but there is no benefit of local treatment over CHT [12)].

Forty-five postradiation therapy Glioblastoma cases were retrospectively identified as having indeterminate MRI findings of progression versus pseudoprogression. The dynamic susceptibility contrast MR images were processed with different software and three different relative CBV metrics based on the abnormally enhancing regions were computed. The intersoftware intraclass correlation coefficients were 0.8 and below, depending on the metric used. No statistically significant difference in progression determination performance was found between the software packages, but performance was better for the cohort imaged at 3.0 T versus those imaged at 1.5 T for many relative CBV metric and classification criteria combinations. The results revealed clinically significant variation in relative CBV measures based on the software used, but minimal interoperator variation. Kelm et al. recommend against using specific relative CBV measurement thresholds for Glioblastoma progression determination unless the same software or processing algorithm is used [13)].

2013

A retrospective study of 47 patients with either newly diagnosed (30 patients) or Glioblastoma recurrence (17 patients) treated with BCNU (bis-chloroethylnitrosourea) wafers. Thirteen of the newly diagnosed patients received local BCNU and irradiation only (first-line BCNU), while 17 patients additionally received concomitant and adjuvant temozolomide (TMZ) radiochemotherapy (first-line BCNU + TMZ). Of the 17 patients treated for Glioblastoma recurrence (second-line BCNU), 16 had received radiotherapy with concomitant and adjuvant TMZ as an initial treatment. Median overall survival (OS) did not significantly differ between 19 patients with MGMT promoter methylated tumors when compared to 28 patients with unmethylated tumors (18.9 vs 15.0 months; $p = 0.1054$). In the first-line BCNU + TMZ group, MGMT promoter methylation was associated with longer OS (21.0 vs 11.1 months, $p = 0.0127$), while no significant survival differences were detected in the other two subgroups. Progression-free survival did not significantly differ between patients with and without MGMT promoter methylated tumors in the entire patient cohort or any of the three subgroups. The first-line BCNU + TMZ group showed no significant difference in OS when compared to the first-line BCNU group (18.9 vs 14.7 months), but tended to have more therapy-related adverse effects (53% vs 24%, $p = 0.105$). In summary, MGMT promoter methylation showed a non-significant trend toward longer survival in our patient cohort. The combination of TMZ radiochemotherapy with local delivery of BCNU did not provide a significant survival benefit compared to local BCNU alone, but was associated with a higher rate of adverse effects. Owing to the small number of patients investigated, however, these findings would need to be corroborated in larger patient cohorts [14)].

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