Stupp protocol

A protocol about the temozolomide combined with radiotherapy treatment for glioblastoma was researched by Roger Stupp in 2005.

The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity [1].

The landmark Stupp study demonstrated a survival advantage with concomitant and adjuvant temozolomide (TMZ) with standard radiotherapy (RT) in glioblastoma multiforme (Glioblastoma) patients but excluded those older than 70 years.

Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival.

A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7 percent of patients.

The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity [2].

Protocol

Radiotherapy

total 60 Gy

2 Gy per daily fraction (Monday to Friday) over 6 weeks

temozolomide

during radiotherapy: 75 mg per square meter of body-surface area per day, 7 days per week post-radiotherapy (adjuvant): six cycles consisting of 150-200 mg per square meter for 5 days during each 28-day cycle

This therapy resulted in a significant survival improvement at 2 years:

26.5% 2-year-survival with Stupp protocol

10.4% 2-year-survival with radiotherapy alone

Interval

The optimal interval between surgery and these adjuvant therapies, and its impact on survival, is unknown. To investigate this, de-identified claims from a large, private health insurance database were queried to identify adult patients who underwent index craniotomy for resection of a supratentorial neoplasm during the period 2005-2014 and began postoperative radiation and temozolomide within 13 weeks of surgery. A total of 2535 patients were assigned to groups based on interval from surgery to first radiation treatment of up to 4 weeks, 4-6 weeks, or 6-13 weeks. Of these, 1098 patients began radiation treatment within 4 weeks of craniotomy, 1019 between 4 and 6 weeks, and 418 between 6 and 13 weeks. There was significant regional variation in treatment schedule in the United States. Survival was calculated based on time from first craniotomy to death. Kaplan-Meier plot and multivariate Cox proportional hazard regression demonstrated a statistically significant association between earliest postoperative radiation and decreased survival (hazard ratio 1.31), along with older age and male sex. Earlier initiation of postoperative radiation for high-grade glioma is not associated with increased survival. Rather, beginning radiation treatment within 4 weeks of craniotomy was associated with significantly worse survival compared to initiation of treatment 4-13 weeks after craniotomy. This is the largest population-based study to date regarding timing of Stupp protocol initiation [3].

Novel Drugs

The use of novel therapeutic agents in combination with the Stupp protocol were all shown to be superior than the Stupp protocol alone for the treatment of newly diagnosed glioblastoma, ranked as follows: cilengitide 2000mg/5/week, bevacizumab in combination with irinotecan, nimotuzumab, bevacizumab, cilengitide 2000mg/2/week, cytokine-induced killer cell immunotherapy, and the Stupp protocol.

In terms of serious adverse effects, the intervention group showed a 29% increase in the incidence of adverse events compared with the control group (patients treated only with Stupp protocol) with a statistically significant difference (RR=1.29; 95%CI 1.17-1.43; P<0.001). The most common adverse events were thrombocytopenia, lymphopenia, neutropenia, pneumonia, nausea, and vomiting, none of which were significantly different between the groups except for neutropenia, pneumonia, and embolism.

All intervention drugs evaluated in the study were superior to the Stupp protocol alone when used in combination with it. However, they could not conclusively confirm whether cilengitide 2000mg/5/week was the optimum regime, as only one trial using this protocol was included in the study [4].

Case series

2017

Contemporary data from 103 consecutive patients with complete imaging and clinical data who underwent resection of newly diagnosed glioblastoma followed by the Stupp protocol between 2010 and 2013 were analyzed. Clinical, radiographic, and outcome parameters were retrieved for each patient, including magnetic resonance imaging (MRI)-based volumetric tumor analysis before, immediately after, and 3 months post-surgery.

OS rate was 17.6 months. A significant incremental OS advantage was noted, with as little as 85 % T1-weighted gadolinium-enhanced (T1Gd)-EOTR measured on contrast-enhanced MRI. Pre- and immediate postoperative FLAIR-based EOTR was not predictive of OS; however, abnormal FLAIR volume measured 3 months post-surgery correlated significantly with outcome when FLAIR residual tumor volume (RTV) was <19.3 cm3 and <46 % of baseline volume ($p < 0.0001$ for both). Age and isocitrate dehydrogenase (IDH)-1 mutation were predictive of OS ($p < 0.0001$, Cox proportional hazards).

OS correlated with the immediate postoperative T1Gd-EOTR measured by enhanced T1 MRI, but not by FLAIR volume. Diminished abnormal FLAIR volume at 3 months post-surgery was associated with OS benefit when FLAIR-RTV was <19.3 cm3 or <46 % of baseline. These threshold values provide a new radiological variable that can be used for prediction of OS in patients with glioblastoma immediately after completion of standard chemoradiation [5)].

Between January 2010 and December 2012, 110 patients with newly diagnosed Glioblastoma underwent surgical removal at the Neurooncology Department of the Clinic Center of Serbia. Patients were divided into 2 groups according to postoperative treatment. Group A (n = 24 patients), treated before January 2011, received adjuvant standard radiation therapy and carmustine (bis-chloroethyl-nitrosourea), and group B (n = 86 patients), treated after January 2011, received postoperative treatment according to the Stupp protocol.

The Stupp protocol had a significant favorable impact on overall survival at 1-year follow-up (79.1% in group B vs. 62.5% in group A; $P = 0.016$); no differences were noted in regard to progression-free survival. Multivariate analysis identified younger age and gross total resection of tumor as positive prognostic factors.

Adoption of the Stupp protocol had a favorable impact on overall survival, but not on progression-free, survival rate. Wider surgical resection involving the peritumoral brain zone, as confirmed by univariate and multivariate analysis, represents the most favorable prognostic factor [6)].

2016

To analyse the pattern of recurrence of patients treated with Stupp protocol in relation to technique, to compare in silico plans with reduced margin (1 cm) with the original ones and to analyse toxicity. 105 patients were treated: 85 had local recurrence and 68 of them were analysed. Recurrence was considered in field, marginal and distant if >80 %, 20-80 % or <20 % of the relapse volume was included in the 95 %-isodose. In silico plans were retrospectively recalculated using the same technique, fields angles and treatment planning system of the original ones. The pattern of recurrence was in field, marginal and distant in 88, 10 and 2 % respectively and was similar in in silico plans. The margin reduction appears to spare 100 cc of healthy brain by 57 Gy-volume ($p = 0.02$). The target coverage was worse in standard plans (pt student < 0.001), especially if the tumour was near to organs at risk ($p\chi 2 < 0.001$). PTV coverage was better with IMRT and helical-IMRT, than conformal-3D (pAnova test = 0.038). This difference was no more significant with in silico planning. A higher incidence of asthenia and leuko-encephalopathy was observed in patients with greater percentage of healthy brain included in 57 Gy-volume. No differences in the pattern of recurrence according to margins were found. The margin reduction determines sparing of healthy brain and could possibly reduce the incidence of late toxicity. Margin reduction could allow to use less sophisticated techniques, ensuring appropriate target coverage, and the choice of more costly techniques could be

reserved to selected cases [7].

Among a total of 101 patients, GTR, STR, PR and stereotactic biopsy was performed in 57 (56.4%), 34 (33.7%), 9 (8.9%) and 1 patient (1%), respectively. Follow-up imaging at the end of Stupp protocol classified 45 patients (44.6%) as Pseudoprogression (psPD) psPD and 56 (55.4%) as non-psPD. psPD was observed in 24 (61.5%) of 39 patients with methylated MGMT promoter and 21 (33.9%) of 62 patients with unmethylated MGMT promoter ($p < 0.01$). psPD was documented in 17 (29.8%), 19 (55.9%), 8 (88.9%) and 1 (100%) patient with GTR, STR, PR and stereotactic biopsy ($p < 0.01$), respectively. On multivariate analysis MGMT promoter status (OR 3.36, 95% CI 1.36-8.34) and EOR (OR 4.12, 95% CI 1.71-9.91) were independent predictors of psPD. A Cox proportional hazards model showed that MGMT status (HR 2.51, $p < 0.01$) and EOR (HR 2.99, $p < 0.01$) significantly influenced survival. MGMT status and EOR have a significant impact on psPD. GTR can reduce the side effects of psPD and prolong survival [8].

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