Clinical Oncology xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

High-dose Neural Stem Cell Radiation May Not Improve Survival in Glioblastoma

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Received 3 August 2016; received in revised form 1 December 2016; accepted 6 December 2016

Abstract

Aims: To evaluate the effect of radiotherapy dose-volume parameters of neural stem cell (NSC) compartment on progression-free survival (PFS) and overall survival after post-resection chemoradiation in newly diagnosed glioblastoma.
Materials and methods: Sixty-one patients with unifocal glioblastoma were included. Ipsilateral (NSC_Ipsi), contralateral (NSC_Contra) and combined NSC (NSC_Combined) were contoured on radiotherapy planning computerised tomography datasets. NSC dose-volume parameters were correlated with PFS and overall survival. Serial magnetic resonance imaging scans were assessed to understand the frequency of pre- and post-treatment involvement of the NSC by contrast enhancing lesions (CELs).
Results: Baseline involvement of NSC with CELs was seen in 67.2% and 95.9% had CELs and FLAIR abnormalities at progression. With a median follow-up of 14.1 months (interquartile range 9.4–20.6 months), median PFS and overall survival were 14.5 (95% confidence interval 11.6–17.5) and 16.2 (95% confidence interval 13.3–19.2) months, respectively. Poor Eastern Cooperative Oncology Group performance score, advanced recursive partitioning analysis class, unmethylated O6-methylguanine methyltransferase (MGMT) status, higher than median of mean NSC_Ipsi dose were associated with significantly inferior PFS and overall survival on univariate analysis. On multivariate analysis, unmethylated MGMT status, higher than median of mean doses to NSC_Ipsi and poor compliance to adjuvant temozolomide were independent predictors of inferior survival.
Conclusions: In this cohort, 67.2% of newly diagnosed glioblastoma patients had NSC involved with CELs at presentation and 95.9% at progression. This might be an imaging surrogate of the current notion of gliomagenesis and progression from NSC rests. A high radiation dose to NSC_Ipsi was significantly associated with inferior survival. This could be a function of larger tumours and planning target volumes in those with pre-treatment NSC involvement. Methylated MGMT and good compliance to adjuvant temozolomide were independent predictors of better survival. Until further evidence brings hope for glioblastoma, elective, partial NSC irradiation remains experimental.

Key words: Glioblastoma; neural stem cell; radiation therapy; survival

Introduction

Glioblastoma is a heterogeneous tumour. The cancer stem cell hypothesis sheds some light on its heterogeneity [1–3]. Studies have documented the presence of neural stem cells (NSC) with astrocyte-like characteristics in the adult human brain [4–8]. The subventricular zone (SVZ) of the lateral ventricles and the subgranular layer (SGL) of the dentate gyrus of the hippocampus in adults represent these stem cell niches. These cells are capable of self-renewal, multipotentiality and gliomagenesis [9–14]. Optimal animal models have suggested that these regions with high-density stem cell populations are sensitive to chemical and viral carcinogenesis compared with other areas of potentially quiescent mammalian brain [15]. The NSC possess cardinal properties of specific lineage hierarchy and plasticity. Similar to other human stem cells they have transiently dividing immediate progenitors capable of tumour initiation and propagation. Molecular determinants of normal neurogenesis seem to be involved in

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http://dx.doi.org/10.1016/j.clon.2017.01.010
0936-6555/

gliomagenesis in certain subsets of glioblastoma and could emerge as potential treatment targets for overcoming inherent resistance to standard chemoradiation [3]. Post-resection care for glioblastoma remains partial brain conformal radiotherapy with concurrent and adjuvant temozolomide (TMZ) based on the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) [16]. Being a highly aggressive tumour, this results in a median overall survival of only 14.6 months [17] with most recurrences in and around the resection cavity.

Magnetic resonance imaging (MRI) morphology of contrast enhancing lesions (CELs) in specific relationship with the SVZ and the cortex has suggested that some glioblastomas may carry radiological signatures of their stem cell origin [17–19]. Elective irradiation of the NSC compartment, as a strategy to eliminate potential stem cell rests and enhance survival, remains experimental with conflicting results [20–26]. A competing therapeutic strategy is NSC sparing irradiation in selected patients with glioblastomas and it aims to respect plasticity for repair, thereby improving neurocognitive outcomes [27].

The aim of this study was to correlate radiotherapy dose-volume parameters of the NSC compartment with progression-free survival (PFS) and overall survival after post-resection chemoradiation in newly diagnosed patients with glioblastoma. Serial MRI scans were assessed to understand the frequency of pre- and post-treatment involvement of the NSC by CELs.

Materials and Methods

Sixty-one patients with newly diagnosed unifocal glioblastoma with available pre- and post-progression MRI, treated with standard fractionated radiotherapy and TMZ-based chemotherapy were included in this analysis. Age, performance status, imaging characteristics, extent of surgery, pathological findings, treatment details and survival were documented from a prospectively maintained electronic database. Accessible radiation planning data and documented event of stable disease, progression or death were prerequisites of eligibility.

Assessment of Pre- and Post-treatment Involvement of the Neural Stem Cell Compartment by Glioblastoma

Pre- and post-progression MRI datasets were reviewed for the location of CELs and non-enhancing FLAIR changes in relationship with the NSC compartment.

Structure Segmentation and Dosimetry

Patients underwent computerised tomography simulation with intravenous contrast in the supine position using a custom-made thermoplastic mask. According to our institutional policy, adjacent computerised tomography slice spacing was 2.5 mm from vertex to base of skull. Treatment planning MRI was fused with the planning computerised tomography. Target and organ at risk volumes were contoured on Varian Eclipse TPS, version 10.2.3. Ipsilateral, contralateral and combined NSC compartments comprising the SVZ and SGL were contoured according to the method published by Barani *et al.* [27]. The SVZ was contoured as a 5 mm strip along lateral ventricular walls and the SGL was the anatomic limit of the dentate gyrus of the hippocampus. Boolean function of the radiotherapy treatment planning software was used to generate ipsilateral (NSC_Ipsi), contralateral (NSC_Contra) and combined (NSC_Combined) NSC volumes as continuous structures. The clinical target volume was a 2 cm margin around the CEL, edited to include FLAIR abnormalities and oedema as a single volume. The planning target volume (PTV) prescription was 59.4–60 Gy at 1.8–2.0 Gy per fraction over 6–6.5 weeks by three-dimensional conformal radiotherapy. The maximum, mean and minimum doses to individual and combined NSC volumes, SVZ and SGL were recorded in Gy from dose-volume histogram data in addition to standard plan evaluation. Partial dose volume parameters of the stem cell rests, although analysed, were not used for purposes of any meaningful interpretation. This was not carried out in keeping with the multipotentiality of cancer stem cells. Any stem cell escaping death is capable of initiating and propagating oncogenesis.

Statistical Analysis

Frequency tables and descriptive analysis were used to analyse patient demography, tumour and treatment characteristics. The Kaplan–Meier method was used to estimate survival. PFS was calculated from the date of diagnosis to the first evidence of clinical or radiological progression. The status at last follow-up or death was considered for overall survival. Death from any cause was considered as an event for overall survival. A Log-rank test was used to test for differences in PFS and overall survival. Factors significant in univariate analysis were tested by multivariate analysis using Cox proportional hazard model. The NSC_Combined dose was not used in the multivariate model because the NSC_Ipsi volume is purely a nested function of the combined NSC volume. All statistical analyses were two-sided at a significance level of 5%. The statistical analysis was carried out using SPSS version 23.0.

Results

Sixty-one patients meeting eligibility criteria were included in this analysis. Table 1 shows patient, tumour and treatment characteristics. The median age was 57 years (interquartile range 44.0–60.5 years) with male preponderance (62.3%). The frontal lobe (32.8%) was the most common location, followed by temporal (31.1%) and parietal (27.9%) lobes. Baseline involvement of NSC with CELs was seen in 67.2%. At progression, 95.9% of patients had involvement of the NSC with CELs and FLAIR abnormalities. Twenty-eight (45.9%) patients underwent gross total excision and O6-methylguanine methyltransferase (MGMT)

Please cite this article in press as: Achari R, et al., High-dose Neural Stem Cell Radiation May Not Improve Survival in Glioblastoma, Clinical Oncology (2017), http://dx.doi.org/10.1016/j.clon.2017.01.010