Journal of Clinical Neuroscience 22 (2015) 785–799

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

A novel literature-based approach to identify genetic and molecular predictors of survival in glioblastoma multiforme: Analysis of 14,678 patients using systematic review and meta-analytical tools

Matthew N.T. Thuy [a,*], Jeremy K.T. Kam [a], Geoffrey C.Y. Lee [a], Peter L. Tao [a], Dorothy Q. Ling [a], Melissa Cheng [a], Su Kah Goh [a], Alexander J. Papachristos [a], Lipi Shukla [a], Krystal-Leigh Wall [a], Nicolas R. Smoll [a], Jordan J. Jones [a], Njeri Gikenye [a], Bob Soh [a], Brad Moffat [b], Nick Johnson [a] Katharine J. Drummond [a]

[a] Department of Neurosurgery, Royal Melbourne Hospital, Parkville, VIC, Australia
[b] Department of Radiology, Royal Melbourne Hospital, Parkville, VIC, Australia

ARTICLE INFO

Article history:
Received 7 September 2014
Accepted 25 October 2014

Keywords:
Adults
Glioblastoma
Meta-analysis
Neurosurgery
Survival
Systematic review

ABSTRACT

Glioblastoma multiforme (GBM) has a poor prognosis despite maximal multimodal therapy. Biomarkers of relevance to prognosis which may also identify treatment targets are needed. A few hundred genetic and molecular predictors have been implicated in the literature, however with the exception of IDH1 and O6-MGMT, there is uncertainty regarding their true prognostic relevance. This study analyses reported genetic and molecular predictors of prognosis in GBM. For each, its relationship with univariate overall survival in adults with GBM is described. A systematic search of MEDLINE (1998–July 2010) was performed. Eligible papers studied the effect of any genetic or molecular marker on univariate overall survival in adult patients with histologically diagnosed GBM. Primary outcomes were median survival difference in months and univariate hazard ratios. Analyses included converting 126 Kaplan–Meier curves and 27 raw data sets into primary outcomes. Seventy-four random effects meta-analyses were performed on 39 unique genetic or molecular factors. Objective criteria were designed to classify factors into the categories of clearly prognostic, weakly prognostic, non-prognostic and promising. Included were 304 publications and 174 studies involving 14,678 unique patients from 33 countries. We identified 422 reported genetic and molecular predictors, of which 52 had $\geqslant$2 studies. IDH1 mutation and O6-MGMT were classified as clearly prognostic, validating the methodology. High Ki-67/MIB-1 and loss of heterozygosity of chromosome 10/10q were classified as weakly prognostic. Four factors were classified as non-prognostic and 13 factors were classified as promising and worthy of additional investigation. Funnel plot analysis did not identify any evidence of publication bias. This study demonstrates a novel literature and meta-analytical based approach to maximise the value that can be derived from the plethora of literature reports of molecular and genetic factors in GBM. Caution is advised in over-interpreting the results due to study limitations. Further research to develop this methodology and improvements in study reporting are suggested.

1. Background

Glioblastoma multiforme (GBM), the most common primary malignant brain tumour, has a very poor prognosis despite maximal multimodality therapy and recent research efforts. The most recent advance, concomitant temozolomide chemoradiation, has increased median survival by 2.5 months and increased the 2 year survival rate by 16% [1]. However despite this, and improvements in surgical resection and targeted radiotherapy, survival rarely exceeds 2 years.

The past decade has witnessed an explosion of research into the prognostic and treatment targeting value of hundreds of genetic and molecular factors in GBM, with the publication of thousands of reports of potential biomarkers related to prognosis, treatment response and treatment targets. For two, there is strong evidence of prognostic value, that is, O6-MGMT promoter hypermethylation, and IDH1/2 mutation. However even for MGMT, some studies have

* Corresponding author.
E-mail address: matthew.thuy@gmail.com (M.N.T. Thuy).

http://dx.doi.org/10.1016/j.jocn.2014.10.029
0967-5868/

reported a significant survival benefit [2,3], but others report a non-significant effect [4–6]. This has been attributed to study differences and a synergistic effect with temozolomide. There have been a large number of reports showing a survival difference with IDH1 mutation [7–11]. There has also been significant interest in other commonly investigated factors, including EGFR, p53, PTEN, CDKN2A and Ki-67 but no consensus yet as to their prognostic value.

Given this context, we undertook a novel literature based approach to identify prognostic factors for adult GBM and to confirm their value. We performed a systematic literature review and meta-analysis of published data to identify potential prognostic biomarkers. We then created specific objective criteria to classify these factors into "clearly prognostic", "weakly prognostic", and "non-prognostic", as well as to identify promising factors. We used a very broad search strategy which identified all English papers with glioblastoma/glioma/astrocytoma combined with survival (and other synonyms), and then carefully excluded irrelevant articles. This methodology, while also having limitations, has significant potential for future analysis of the subsequent even more voluminous literature in this arena. We aimed to demonstrate how such an approach, when properly refined, could guide future research efforts, possibly more efficiently. There is no doubt much more needs to be done to improve the survival for patients with GBM. While this review focussed on prognostic biomarkers related to survival, a similar methodology could be used to determine treatment targets, which may be distinct.

2. Methods

2.1. Inclusion criteria

Studies were eligible for inclusion if they met the following criteria:

- Prospective cohort studies, retrospective cohort studies, case series, or analysis of clinical trial patients examining prognosis.
- Studied a group or subgroup of primarily adult patients with only histologically diagnosed GBM. If any non-GBM pathology was present in the group or subgroup, the study was excluded. This also excluded "radiologically diagnosed GBM" without histological diagnosis.
- Studied the relationship of $\geqslant 1$ genetic or molecular factor(s) with univariate overall survival.
- Published between 1 January 1998 and 1 July 2010.
- English language article, human subjects.

2.2. Search strategy

MEDLINE (1950–28 June 2010) was searched on 7 July 2010 using the ISI Web of Knowledge search engine. The search strategy was as follows:

TI=(prognos* OR surviv* OR mortalit* OR death OR "fatal outcome")

AB=(prognos* OR surviv* OR mortalit* OR death OR "fatal outcome")

MH=(Survival OR Mortality OR "Kaplan-Meiers Estimate" OR Death OR "Fatal Outcome" OR Prognosis)

#1 OR #2 OR #3

TI=(glioblastoma OR glioma OR astrocytoma)

AB=(glioblastoma OR glioma OR astrocytoma)

MH=(Glioma OR Astrocytoma OR Glioblastoma)

#5 OR #6 OR #7

#4 AND #8

#9 AND Language=(("Eng")) AND Species=(("humans"))

Additional publications were also identified by searching reference lists of included publications.

2.3. Application of the inclusion criteria

One author (M.T.) reviewed the titles and abstracts of all publications identified and excluded all articles clearly not meeting the inclusion criteria. The full-text of the remaining publications was obtained, and one author (M.T.) excluded all articles clearly not meeting the inclusion criteria. Following this, the full text of the remaining articles were reviewed by two authors, the primary author (M.T.) and another (one of J.K., G.L., P.T., N.S., N.G., D.L., M.C., J.J., S.K.G., K.L.W., A.P., L.S., B.S., B.M., and N.J.) and included or excluded. Where there was any doubt regarding inclusion status, this was discussed between authors, with a third author (K.J.D.) acting as the final arbitrator.

2.4. Data extraction

Data were extracted using a standardised form in either Microsoft Access (Microsoft, Redmond, WA, USA) or Openoffice.Org Base by one author (M.T., J.K., G.L., P.T., N.S., D.L., M.C., S.K.G., K.L.W., A.P., L.S., B.S., B.M., N.J.) and checked by at least one other author (M.T., J.K., G.L., P.T., D.L., M.C., S.K.G., A.P., L.S., B.S., K.L.W.). Study authors were contacted by email (M.T.) if there were missing data and further data relating to their studies were obtained from Professor P. Korkopoulou, Professor M. Weller and Dr P. Sminia.

2.5. Primary outcomes

The primary outcomes of interest were median survival difference (MSD) between groups in months and univariate hazard ratios (HR). These statistics, when available, were obtained from the text of the article. Where not readily available these were calculated from available Kaplan–Meier curves and raw data sets published, or obtained from authors. Where univariate HR were not available from the text but raw patient data sets were available, HR were obtained through the R statistical software, survival package. Where univariate HR were not available from the text or raw data, a univariate HR was obtained via measurements from Kaplan–Meier curves using previously published methods [12] with statistician support (Dr Sandy Clarke).

2.6. Data analysis

Random-effects weighted meta-analyses were performed when the MSD and its standard error were able to be calculated in two or more studies, or when the natural log of the hazard ratio and its standard error were able to be calculated in two or more studies. All forest plots were assessed for potential heterogeneity, both visually and numerically. Funnel plot analysis was performed in factors with 10 or greater studies to assess for possible publication bias. Meta-analyses were performed using R statistical software [13], rmeta package [14]. PASW Statistics 18 was used to create summary plots of the meta-analyses. All meta-analyses were reviewed by two experts in brain tumour biology (Dr Giovanna D'Abaco, Dr Theo Mantamadiotis) to ensure biological appropriateness. All prognostic factors with two or more studies were then classified as clearly prognostic, weakly prognostic, non-prognostic and promising using objectively defined criteria incorporating elements of generalisability (number of studies), precision (p values) and clinical effect (MSD and HR).