Journal of the Neurological Sciences 405 (2019) 116431

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Letter to the Editor

Lack of development of *Pneumocystis jirovecii* Pneumonia in a cohort of 103 Italian glioblastoma patients not receiving prophylaxis during post-surgical chemoradiotherapy

ARTICLE INFO

Keywords:
Glioblastoma
Pneumocystis jirovecii Pneumonia
Myelotoxicity
Antibiotic prophylaxis

Patients diagnosed with high grade gliomas (HGG) usually receive surgery, radiation, temozolomide (TMZ) and corticosteroids [1]. A major concern in patients who receive chemoradiotherapy (CRT) is the risk of developing secondary myelosuppression and a related infection during treatment [2], which in turn may lead to discontinuation of anti-tumor therapy and possibly to a worse outcome, although this is not unequivocally documented.

CRT may also lead to a long-lasting reduction of WBC, associated with early death from tumor progression [2].

Myelosuppression is a dose-limiting toxicity of most cytotoxic chemotherapies, including TMZ. The overall incidence for grade 3–4 myelotoxicity (including thrombocytopenia, neutropenia, lymphopenia, and rare occurrence of aplastic anaemia) [3] is controversial. In fact, an overall incidence for myelotoxicity has been reported in 5–8% [3] to 40% of patients [4].

Among treatment-related infections, *Pneumocystis jirovecii* Pneumonia (PJP) has been reported in 2 out of 15 glioblastoma (GBM) patients in a phase I-II trial [5]; since then, PJP prophylaxis has been required by the FDA after approval of the Stupp schedule. However, evidence for PJP during CRT is very limited and the rate of PJP still low even if the patients have multiple risk factors in addition to the use of CRT. For this reason, there is no consensus on the use of Pneumocystic prophylaxis for patients receiving temozolomide for GBM or high-grade glioma patients [6]. Moreover, adverse events are associated with the use of PJP prophylaxis. As a consequence, a recent meta-analysis suggests PJP prophylaxis only when risk of PJP is > 3.5% [7].

The objective of our study was to investigate the types of infection contracted on CRT and in particular if the absence of a proper PJP prophylaxis led to an increased rate of PJP. Moreover, we evaluated the association between CRT and lymphopenia, then whether severe reductions in WBC were related to early death from tumor progression or greater risk of developing documented infections.

We performed a retrospective, Institutional Review Board-approved cohort study in 103 patients (60 men and 43 women), who were consecutively diagnosed with GBM in “A. Manzoni” Hospital in Lecco during the period May 2007 to December 2013. The patients were all adults, with a mean age at the diagnosis of 61.7 years (range 31–79 years). All of these patients were treated with CRT according to the Stupp protocol without PJP prophylaxis. Mean survival time was 18.4 months (range 3.3 to 92 months). Significant co-medication included steroid use (i.e. dexamethasone at a dose of > 3 mg/day for at least 4 weeks) in 65% of the patients.

Haematological toxicities of CRT were assessed according to Common Terminology Criteria for Adverse Events (CTCAE, version 5.0; November 27, 2017). Lymphocyte count was measured weekly during concomitant chemoradiotherapy and then at 2–3 and 4 weeks after each adjuvant Temozolomide cycle throughout the duration of the treatment.

In our 103 patients receiving CRT, 18% developed grade 3–4 lymphopenia (11.4% grade 3, 6.6% grade 4). In this group of patients, mean survival was 17.5 months (compared to 18.4 months of the general group) and 3 of them developed an infective complication during CRT (1 community-acquired pneumonia and a herpes simplex virus, 1 herpes zoster and 1 fever without a source) (Fig. 1).

Among all the 103 subjects enrolled, a total of 9 patients (8.7%) had documented infectious complications during the CRT, as they are listed in detail in Table 1. It is interesting to note that lymphocytopenia was seen in 7 of these 9 patients and, as mentioned above, in 3 of them it was severe. In this group of individuals, the infectious complications had been developed at a median time of 2.3 months after the beginning of CRT and, according to our findings, the difference in the mean survival time was not significant in comparison with patients not developing infections.

However, no one of these patients was diagnosed as PJP, despite PJP prophylaxis was not given as it would be necessary according to the existing guidelines.

Overall, our results confirm those reported by Neuwelt and coworkers in a different retrospective study, where < 1% of 127 patients with glioblastoma treated with standard chemoradiotherapy without PJP prophylaxis developed PJP [6].

Furthermore, in our cohort, infectious complications were more frequent in patients developing grade 3–4 lymphocytopenia, but, exactly as described by Grossman [2] this did not translate into a significantly shorter overall survival. However, only 18% were significantly lymphopenic and this precludes any firm statements on this last aspect.

Moreover, we can only speculate that a lower percentage of our patients receiving steroids (65% versus 82%) and a lower cumulative

https://doi.org/10.1016/j.jns.2019.116431
Received 31 May 2019; Received in revised form 16 July 2019; Accepted 19 August 2019
Available online 20 August 2019
0022-510X/

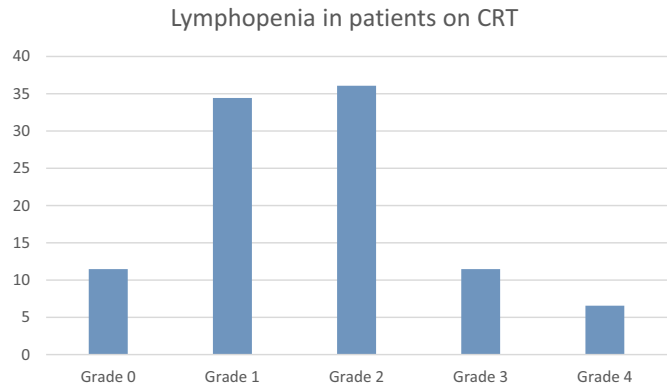

Fig. 1. Lymphopenia in patients on CRT.

Table 1
Incidence of infectious complication during chemoradiotherapy.

Incidence of infections	
Infection	Number of patients
Community acquired pneumonia	3
Fever without source	3
Urinary tract infection	2
Herpes Zoster	1
Herpes simplex 1	1
Phlegmon	1
Purulent otitis	1

dose compared with Grossman's [2] may partly explain why we reported a lower frequency of infections overall. In fact, prolonged high-dose steroid use together with CRT have been described as significant risk factors for PJP development [8].

It is also well-reported that PJP rates may significantly vary by geographical distribution [9], although no exhaustive epidemiological data are available for Italy. Furthermore, trimethoprim/sulfamethoxazole became part of current standard of care after 2002 when a monocentric trial reported PJP in 2 out of 15 patients with GBM treated with CRT [5]. For this reason, we probably need more studies pointing out the incidence of PJP during CRT in different populations from different countries in order to better understand the role of PJP prophylaxis.

On the other hand, PJP has an overall mortality rate of 35–55%. However, the exact incidence in solid tumors still remains unknown [8]. Despite that, the role of prophylaxis remains debated and may be probably warranted only in selected patients based on careful consideration of the risk/benefit ratio.

In conclusion, our data run counter to current standard of care and seem to support a lack of undisputable evidence for a favourable risk/benefit profile in the use of PJP prophylaxis for all newly diagnosed GBM patients undergoing the Stupp schedule, also considering the rate of side effects (15.2%) and severe adverse reactions (around 3%, mainly leukopenia) in non-HIV adults receiving trimethoprim/sulfamethoxazole for prolonged periods [7] and the need to minimize antibiotic use in an era of increasing multidrugresistant organisms.

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