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Review article

Guidelines, "minimal requirements" and standard of care in glioblastoma around the Mediterranean Area: A report from the AROME (Association of Radiotherapy and Oncology of the Mediterranean arEa) Neuro-Oncology working party

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Contents

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ABSTRACT

Glioblastoma is the most common and the most lethal primary brain tumor in adults. Although studies are ongoing, the epidemiology of glioblastoma in North Africa (*i.e.* Morocco, Algeria and Tunisia) remains imperfectly settled and needs to be specified for a better optimization of the neuro-oncology healthcare across the Mediterranean area and in North Africa countries.

Abbreviations: OS, overall survival; PFS, progression-free survival; WHO, World Health Organization; MA, Mediterranean area; AROME, association of radiotherapy and oncology of the Mediterranean area; MTDs, multidisciplinary teams meetings; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; MRS, magnetic resonance spectroscopy; TMZ, temozolomide; KPS, Karnofsky prognostic index; MGMT, Methylation of the O6-methylguanine-DNA methyltransferase; RTOG, Radiation Therapy Oncology Group; EBRT, external beam radiotherapy; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; GPN, gross natural product; EMR, Eastern Mediterranean Region; UK NICE, United Kingdom National Institute of Clinical Excellence; IOG, improving outcomes guidance.

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Over the last years significant therapeutic advances have been accomplished improving survival and quality of life of glioblastoma patients. Indeed, concurrent temozolomide-radiotherapy (temoradiation) and adjuvant temozolomide has been established as the standard of care associated with a survival benefit and a better outcome.

Therefore, considering this validated strategy and regarding the means and some other North Africa countries specificities, we decided, under the auspices of AROME (association of radiotherapy and oncology of the Mediterranean area; www.aromecancer.org), a non-profit organization, to organize a dedicated meeting to discuss the standards and elaborate a consensus on the "minimal requirements" adapted to the local resources. Thus, panels of physicians involved in daily multidisciplinary brain tumors management in the two borders of the Mediterranean area have been invited to the AROME neuro-oncology working party.

We report here the consensus, established for minimal human and material resources for glioblastoma diagnosis and treatment faced to the standard of care, which should be reached. If the minimal requirements are not reached, the patients should be referred to the closest specialized medical center where at least minimal requirements, or, ideally, the standard of care should be guaranteed to the patients.

1. Introduction

Glioblastoma is the most common and the most aggressive primary malignant brain tumor in adults. In Europe and US, approximately 4000 new cases are diagnosed each year with an incidence of about 3 to 7/100000 habitants. Median age at diagnosis is 64 years and male to female sex ratio is 1,6 (Dolecek et al., 2012; Rachet et al., 2008). In France 2400 new cases are diagnosed each year. The incidence is about 4 to 7/100000 habitants (Badi et al., 2010).

Epidemiology of glioblastomas in North Africa countries (*i.e.* Morocco, Algeria and Tunisia) remains imperfectly settled. Indeed, in the literature, studies depicting epidemiology of brain tumors in North Africa are lacking.

Based on clinical course of the disease, two major forms of glioblastoma are individualized: (i) primary or *de novo* and (ii) secondary glioblastoma. The last, results from tumor progression of an already diagnosed lower grade glioma (*i.e.* WHO [World Health Organization] grade II or III) while primary or *de novo* glioblastoma occurs spontaneously without any previous history of lower grade tumor. *De novo* or primary glioblastoma represent approximately 90% of all glioblastomas (Ohgaki and Kleihues, 2013) and develop in elderly patients.

Although the prognosis of primary glioblastoma remains dismal, over the last decade, significant therapeutic advances have been reached in its management leading to an increase of survival and better quality of life. These advances have been accomplished in terms of tumor staging (*i.e.* clinical, radiological, pathological and molecular), symptomatic treatments (*i.e.* anti-epileptic drugs, steroid therapy), supportive care and in anti-tumor treatments (surgery, radiotherapy, and cytotoxic chemotherapy). Therefore, these progresses should be implemented and benefit to patients in limited resources countries and emergent countries such as North Africa.

We report here the conclusions of the AROME (Association of Radiotherapy and Oncology of the Mediterranean Area; www.aromecancer.org) neuro-oncology working party that involved experts from north and south borders of the Mediterranean area (MA). These conclusions are structured as "minimal requirements and standards" for appropriate medical management of glioblastoma patients based on evidences-based medicine data and expert agreements. This AROME concept of guidelines has been already published for several cancers in 2010 (AROME, 2011).

2. Material and methods

2.1. AROME concept

AROME is a non-profit medical organization aiming to increase collaboration of oncologists and other health care professionals implied in cancer care around the MA. The scope of the Association is to recognize the special circumstances and issues in the MA, to discuss and acknowledge openly existing issues in order to improve the existing problems, with a particular interest for overcoming disparities in cancer care by various actions. Thus, AROME's special focus is to promote practical education and training for all professionals involved in cancer care in the MA courtiers.

2.2. Aims and scope of AROME guidelines

In summary, in the first AROME meeting held in Naples in April 2007, oncologists around the MA met and presented epidemiologic data from their respective countries. This was the first step for the recognition of the specific epidemiologic characteristics in the area, followed by another step of presenting and recognizing the availability of means to provide cancer care in the various countries. Ultimately it became evident that optimum means were not available in several countries, which led to the recognition of the fact that cancer care should be reevaluated and guidelines for treating specific cancer sites should be revisited, since they are inapplicable for several countries in MA. In 2010, we published the first "AROME guidelines for cancer care around the Mediterranean Area" a formalized consensus. These guidelines were structured as *minimum requirements* that should be proposed consisting of the minimal actions any oncologist should be able to perform anywhere in order to provide the acceptable minimum cancer care. On the other hand they aimed to rationalize cancer care and make better management of the available means so as to treat more patients in a most cost-effective manner. Furthermore, they aimed to become a useful tool for providing evidence that optimum care is achievable and to inspire pieces of action in this direction to increase the cancer care to a higher level (AROME, 2011).

2.3. Neuro-oncology working party

In the previous work (AROME, 2011), minimal requirements and standards in neuro-oncology have not been planed. Thus, we decided to dedicate a specific meeting inviting the first AROME

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