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ORIGINAL RESEARCH

Assessment of the management of carcinomatous meningitis from breast cancer globally: a study by the Breast International Group Brain Metastasis Task Force☆

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Background: Carcinomatous meningitis (CM) is a severe complication of breast cancer. The Breast International Group (BIG) carried out a survey to describe the approach to CM internationally.

Patients and methods: A questionnaire on the management of CM was developed by the Brain Metastases Task Force of BIG and distributed to its groups, requesting one answer per group site.

Results: A total of 241 sites responded, 119 from Europe, 9 from North America, 39 from Central/South America, 58 from Asia, and 16 in Australia/New Zealand, with 24.5% being general hospitals with oncology units, 44.4% university hospitals, 22.4% oncology centers, and 8.7% private hospitals. About 56.0% of sites reported seeing <5 cases annually with 60.6% reporting no increase in the number of cases of CM recently. Nearly 63.1% of sites investigate for CM when a patient has symptoms or radiological evidence, while 33.2% investigate only for symptoms. For diagnosis, 71.8% of sites required a positive cerebrospinal fluid cytology, while magnetic resonance imaging findings were sufficient in 23.7% of sites. Roughly 97.1% of sites treat CM and 51.9% also refer patients to palliative care. Intrathecal therapy is used in 41.9% of sites, mainly with methotrexate (74.3%). As many as 20 centers have a national registry for patients with breast cancer with central nervous system metastases and of those 5 have one for CM. Most (90.9%) centers would be interested in participating in a registry as well as in studies for CM, the latter preferably (62.1%) breast cancer subtype specific.

Conclusions: This is the first study to map out the approach to CM from breast cancer globally. Although guidelines with level 1 evidence are lacking, there is a high degree of homogeneity in the approach to CM globally and great interest for conducting studies in this area.

Key words: breast cancer, carcinomatous meningitis

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INTRODUCTION

Carcinomatous meningitis (CM) is a severe complication of breast cancer.[1] It is usually suspected when the patient presents with multiple cranial nerve symptoms, headache, vomiting, or nuchal rigidity, and diagnosis is either made by lumbar puncture and positive cerebrospinal fluid (CSF) cytology or by contrast-enhanced magnetic resonance imaging (MRI) showing uptake in the meninges. Lesions may cause disruption of the CSF flow, which means that CSF cytology must sometimes be repeated (up to three times) before declared negative.[2] It is clinically associated with a rapid deterioration and a poor survival once diagnosed.[1] In recent years, the rate of oligosymptomatic cases has increased as a consequence of increased use of brain MRI either in extension studies of clinical trials or by routine practice.[3] Management of CM includes systemic therapy, radiotherapy (RT), and intrathecal administration of anticancer agents, most frequently methotrexate. Because of the relative rarity (3%-5% of breast cancers)[4] of the condition, as well as the severity and the poor prognosis, very few prospective studies have been performed specifically in this setting, while the frequently poor performance status of patients diagnosed with CM makes undertaking and recruiting to such studies challenging.[5]

As survival times increase in metastatic breast cancer (MBC), the number of patients with CM is expected to increase further. The development of active therapeutic options for patients with CM is an unmet clinical need. To determine the best approach to the disease, the mapping of international practice regarding diagnosis and management, including options such as palliative care, is needed as an initial step to help inform and optimize trial development. Given this, the Brain Metastasis Task Force of the Breast International Group (BIG) developed a survey to understand the current management of CM at a global level.

METHODS

The Brain Metastasis Task Force of BIG created a questionnaire including questions related to epidemiology, diagnosis, and management of CM. The questionnaire (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100483) was distributed to all BIG-affiliated groups, which in turn distributed the questionnaire to their participating sites requesting one answer per site, to be completed between 6 November 2020 and 1 January 2021. The questionnaire contained both binary and open questions. The open questions were few and the answers are entertained in the discussion. The majority of questions were binary questions and were analyzed using descriptive statistics reporting frequencies and percentages. Data were analyzed according to institution type (general hospital with oncology unit, oncology centers, private hospital, and teaching hospital) and geographical location (Asia, Australia/New Zealand, Central and South America, Europe, and North America). Collected data were analyzed by the Brain Metastasis Task Force biostatistician (MJE) using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC).

RESULTS

The questionnaire was answered by physicians at 241 sites from 25 BIG-affiliated groups. Most responses were from Europe (119 sites, 49.4%). Number of sites from the other areas were 9 in North America (7 in Canada and 2 in the United States), 39 in Central and South America (Argentina, Brazil, Chile, Colombia, Mexico, and Peru), 58 in Asia, and 16 in Australia/New Zealand (Figure 1 and Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100483).

Institutions responding to the questionnaire were teaching hospitals (44.4%), general hospitals with an oncology unit (24.5%), oncology centers (22.4%), and private hospitals or clinics (8.7%; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100483). In general, each site treated only few patients with CM per year and only 44.0% of the sites see five or more cases yearly (Table 1, see data under 'Number of CM cases seen annually'). North America (5 sites out of 9) and Europe (60 sites out of 119) saw slightly more CM than the other regions (15 sites out of 39 in South and Central America, 21 sites out of 58 in Asia, and 5 sites out of 16 in Australia/New Zealand). Almost 61% of the sites did not observe an increase in the cases of CM at their respective centers (Table 1, see data under 'Increase over time of cases of CM').

Diagnosis

Investigation for suspected CM in patients with breast cancer was initiated in the majority of centers (63.1%) when patients presented with symptoms such as headache, photophobia, random cranial nerve signs, vomiting, nuchal rigidity, and back pain or had CM-specific MRI findings even without symptoms. One-third (33.2%) of the centers investigated for CM only if the patient had symptoms. This latter practice was more common in Asia (51.7%) compared with all other geographical regions. Usually, in North America (77.8%), Europe (70.6%), and Australia/New Zealand (68.8%), a combination of MRI findings and clinical symptoms prompted an investigation for CM. MRI findings were the only trigger for CM-directed investigation in a very small number of centers (1.7%).

Diagnosis of CM was established by both CSF and MRI in the vast majority of European (82.4%), North American (77.8%), and Central and South American (69.2%) sites, whereas in Australia/New Zealand and Asia these numbers were lower (56.3% and 55.2%, respectively), with a higher rate of patients (43.7% and 39.7%, respectively) being diagnosed by MRI only. Overall, use of both CSF and MRI was reported by 71.8% of centers, and similarly so by the various types of institutions (76.2% of private hospitals, 73.8% of teaching institutions, 70.4% of oncology centers, and 67.8% of general hospitals; Table 2). Nine (3.7%) sites diagnosed CM with CSF cytology only, and five of those repeated CSF three times or more before ruling it out. Of the nine centers that routinely assessed CSF, six would also assess CSF protein and glucose besides cytology (three in

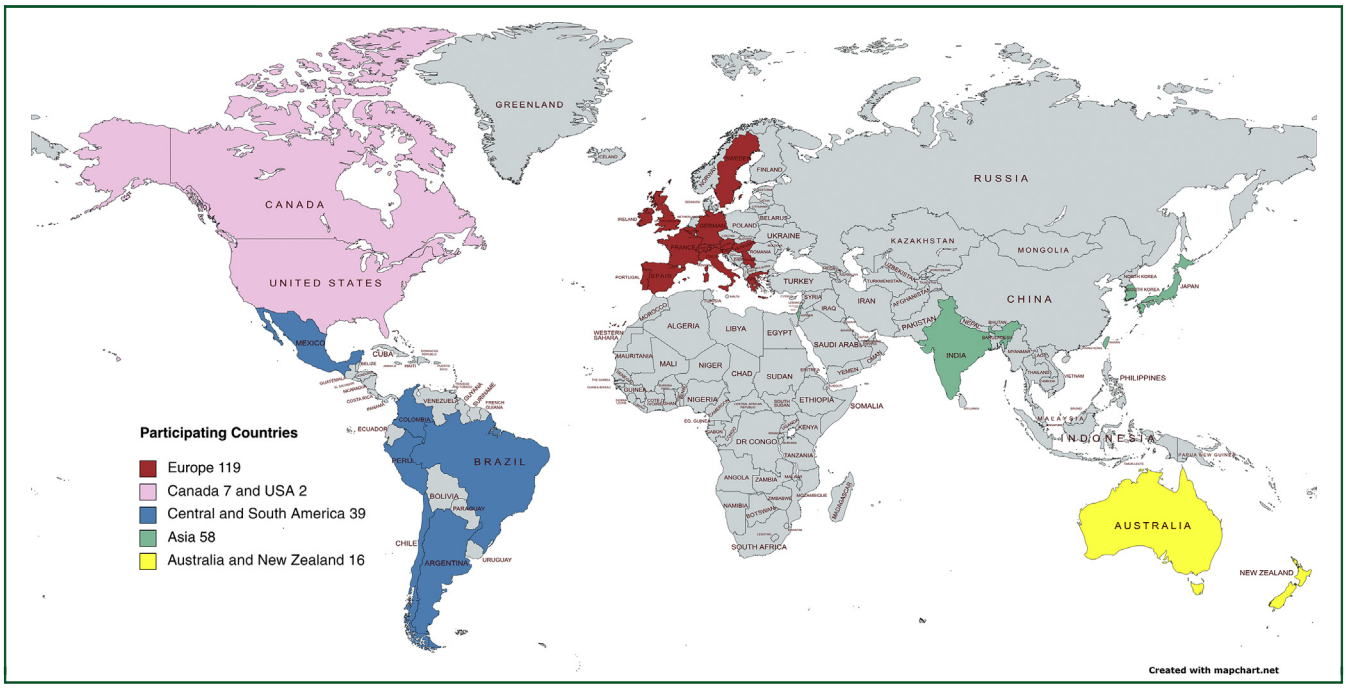

Figure 1. **Map of participation countries.**

academic institutions, two in oncology centers, and one private hospital). Only one site routinely evaluated cancer markers and lactate dehydrogenase in the CSF.

Medical treatment

Almost all sites (234, 97.1%) treated CM from breast cancer while of the 7 sites that did not, 3 referred patients for therapy to a neuro-oncologist and all 7 referred the patients to palliative care. Intrathecal therapy was used in 101 (41.9%) sites: 60 (50.4%) in Europe, 18 (46.2%) in Central and South America, 5 (31.3%) in Australia/New Zealand, 16 (27.6%) in Asia, and 2 (22.2%) in North America. Regarding the type of institution, use of intrathecal therapy was reported by 47.6% of private hospitals, 44.9% of teaching hospitals, 40.7% of oncology centers, and 35.6% of general hospitals with an oncology unit (Table 3). Of the 101 sites that use intrathecal therapy, methotrexate was the agent most commonly employed in 75 (74.3%) sites. Other drugs were used in rare occasions and included trastuzumab in 13 (12.9%) sites, mostly in Europe and in teaching hospitals, liposomal cytarabine in 11 (10.9%) sites, mostly in Europe and mostly in teaching hospitals, and less so, thiotepa 2 (2.0%) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100483).

In the 101 sites that used intrathecal therapy, the drug was infused exclusively through an intraventricular catheter (Ommaya reservoir) in 20 (19.8%) sites while 40 (39.6%) used a lumbar puncture exclusively and the rest 41 (40.6%) used either a reservoir or a lumbar puncture (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100483). Only 14 sites checked CSF flow first, somewhat more often in general hospitals with oncology units. CSF flow was checked with a contrast study in six sites (only in Asia and Latin America) and with a nuclear study in eight sites.

CM therapy was guided by breast cancer subtype in 63.5% of all centers although with some variation, with 69.7% in Europe, 62.5% in Australia, 58.6% in Asia, 56.4% in Central and South America, and 44.4% in North America. The distribution according to type of center that took breast cancer subtype into account when planning treatment was private hospitals (76.2%), oncology centers (72.2%), teaching hospitals (61.7%), and general hospitals with oncology units (54.2%). Clinical parameters weighed very heavily in all treatment decisions regarding CM in 97.5% of centers, irrespective of geographic region and type of institution (Table 4). More specifically, symptoms, systemic tumor burden, presence of parenchymal central nervous system (CNS) disease, performance status, prognosis, and patient

Table 1. **Number of CM cases seen annually and increase of CM cases over time**

	General hospital oncology unit (n = 59), n (%)	Oncology center (n = 54), n (%)	Private hospital (n = 21), n (%)	University hospital (n = 107), n (%)	Total (n = 241), n (%)
Number of CM cases seen annually					
<5	38 (64.4)	22 (40.7)	15 (71.4)	60 (56.1)	135 (56.0)
5-10	21 (35.6)	23 (42.6)	6 (28.6)	36 (33.6)	86 (35.7)
>10	0 (0)	9 (16.7)	0 (0)	11 (10.3)	20 (8.3)
Increase over time of cases of CM					
No	37 (62.7)	33 (61.1)	12 (57.1)	64 (59.8)	146 (60.6)
Yes	22 (37.3)	21 (38.9)	9 (42.9)	43 (40.2)	95 (39.4)

CM, carcinomatous meningitis.

Table 2. Methods used to diagnose CM

	General hospital oncology unit ($n = 59$), *n* (%)	Oncology center ($n = 54$), *n* (%)	Private hospital ($n = 21$), *n* (%)	University hospital ($n = 107$), *n* (%)	Total ($n = 241$), *n* (%)
Both CSF and MRI	40 (67.8)	38 (70.4)	16 (76.2)	79 (73.8)	173 (71.8)
CSF only	0 (0)	5 (9.2)	1 (4.8)	3 (2.8)	9 (3.7)
Clinically only	0 (0)	2 (3.7)	0 (0)	0 (0)	2 (0.8)
MRI	19 (32.2)	9 (16.7)	4 (19.0)	25 (23.4)	57 (23.7)

CM, carcinomatous meningitis; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

preference all contributed to the decision-making process at all types of centers and in all regions. Toxicity from intrathecal methotrexate was reported only in 54 (53.5%) centers, out of the 101 sites using intrathecal therapy for CM, with higher rates in Australia/New Zealand centers ($n = 4$, 90%), but otherwise evenly distributed throughout types of institutions and geographic areas (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100483). The reported toxicity in patients treated with intrathecal therapy in the 54 sites was as follows: only neurological ($n = 13$, 24.1%); only hematological ($n = 7$, 13.0%); both hematological and neurological ($n = 10$, 18.5%); hematological and mucositis ($n = 9$, 16.7%); hematological, mucositis, and neurological ($n = 6$, 11.1%), while other side-effects, including renal toxicity, were rare and reported in less than 10% of sites. About 88% of centers did not combine RT concurrently with intrathecal therapy and this practice was uniformly used in all different types of institutions and different geographical areas.

Radiotherapy

Overall, 88.4% of sites used RT, mostly for localized CM treatment: 95.2% of private sites, 90.7% of oncology centers, 89.7% of teaching hospital sites, and 81.4% of general hospitals with oncology units (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100483). Usually, RT was used for areas of compression and those causing symptoms, although RT of the whole neuraxis was given in 22.1% of sites, most in Europe, Central and South America, and Asia, a practice least adopted by teaching institutions (14.6%; Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100483). The presence of a clinical oncologist in the center was not significantly associated with the use of RT.

Follow-up

During follow-up of therapy, 128 centers repeated CSF cytology. Among the sites that repeated CSF cytology, there were differences in the frequency of CSF testing, with 34 (26.6%) repeating the CSF cytology weekly while the patient was on therapy. Other schedules were also used, such as monthly 35 (27.3%) and biweekly 24 (18.8%).

MRI was used to follow patients on therapy in 136 (56.4%) centers [13 (61.9%) private hospitals, 33 (61.1%) oncology centers, 32 (54.2%) general hospitals, and 58 (54.2%) teaching hospitals]. This approach was encountered in 74 (62.2%) European centers, 9 (56.3%) Australian/New Zealand centers, 20 (51.3%) of Central and South American centers, 29 (50.0%) of Asian centers, and 4 (44.4%) North American centers.

Palliative care

Nearly 93.8% of centers in Australia/New Zealand, 64.1% in Central and South America, 48.3% in Asia, 45.4% in Europe, and 33.3% in North America referred all patients with CM to palliative care for an overall 51.9% referral rate. In terms of the type of institution, 57.6% of general hospitals with oncology unit, 57.4% of oncology centers, 57.1% of private hospitals, and only 44.9% of teaching hospitals referred patients with CM to palliative care.

Research and registry

In all types of institutions and in all geographical areas, a registry for CM or CNS metastases was rare. Specifically, 91.7% of centers did not have a registry for CNS metastasis from breast cancer and of the few that did ($n = 20$), 15 did not have a specific registry for patients with CM. Thus, five centers worldwide, one in Europe, another in Central/South America, and three in Asia, had a registry for CM from breast cancer. Almost all centers were interested in participating in a registry for CM from breast cancer (95.5%), and this answer was uniform and irrespective of geographic region and type of institution.

The vast majority (90.9%) of the centers were interested in participating in a prospective study for patients with CM from breast cancer and this answer was again consistent

Table 3. Intrathecal therapy use

	General hospital oncology unit ($n = 59$), *n* (%)	Oncology center ($n = 54$), *n* (%)	Private hospital ($n = 21$), *n* (%)	University hospital ($n = 107$), *n* (%)	Total ($n = 241$), *n* (%)
No	38 (64.4)	32 (59.3)	11 (52.4)	59 (55.1)	140 (58.1)
Yes	21 (35.6)	22 (40.7)	10 (47.6)	48 (44.9)	101 (41.9)

Table 4. Decision criteria for treatment

	General hospital oncology unit ($n = 59$), *n* (%)	Oncology center ($n = 54$), *n* (%)	Private hospital ($n = 21$), *n* (%)	University hospital ($n = 107$), *n* (%)	Total ($n = 241$), *n* (%)
Is the treatment decision for patients with CM based on breast cancer subtypes?					
No	27 (45.8)	15 (27.8)	5 (23.8)	41 (38.3)	88 (36.5)
Yes	32 (54.2)	39 (72.2)	16 (76.2)	66 (61.7)	153 (63.5)
Is the treatment decision for patients with CM based on clinical parameters?					
No	1 (1.7)	2 (3.7)	1 (4.8)	2 (1.9)	6 (2.5)
Yes	58 (98.3)	52 (96.3)	20 (95.2)	105 (98.1)	235 (97.5)

CM, carcinomatous meningitis.

among different regions and center types, although a slightly lower interest was reported from private hospitals (76.2%). The reported number of patients that could be enrolled at each site were 5-10 patients (22.4%), <5 patients (74.9%), and >10 patients (2.7%) annually. About 89.0% of centers would be willing to collect CSF for the analysis of circulating tumor DNA or other molecular analysis as part of the study. This number was higher in Europe (92.8%), Australia/New Zealand (92.3%), and Central and South America (89.2%), and numerically lower in North America (83.3%) and Asia (80.8%). In terms of willingness to collect CSF for further analysis according to type of institution, private hospitals (81.3%) and general hospitals with oncology units (81.8%) were less willing, while teaching hospitals (92.9%) and oncology centers (91.8%) were more prepared to do so.

The majority of institutions (62.1%) were interested in running subtype-specific prospective CM studies. Respective numbers were highest in Australia/New Zealand (69.2%), followed by Europe (64.0%), Central and South America (62.2%), Asia (57.7%), and North America (50.0%). The corresponding figures according to type of institution were general hospitals (65.5%), oncology centers (63.3%), teaching hospitals (60.6%), and private hospitals (56.3%). Various reasons were given for sites not being able to participate in subtype-specific studies or not preferring those, and the most common reason was not seeing enough patients to be able to enroll in a subtype-specific study.

DISCUSSION

Improvements in the systemic therapy for MBC have resulted in improved outcomes for patients with estrogen receptor-positive and human epidermal growth factor receptor 2 (HER2)-positive breast cancers, and more recently triple-negative breast cancer.[6] Our survey attempted to map out the landscape of CM from breast cancer management globally, to facilitate appropriate clinical trial design to improve outcomes in this area as well.

Our main finding was that despite the lack of level 1 evidence, CM management in patients with breast cancer is remarkably homogeneous worldwide. Furthermore, in the BIG groups there is considerable interest in conducting studies in the field.

Theoretically, CM will be diagnosed more frequently in years to come because of longer survival and earlier as a result of increased use of cross-sectional imaging with MRI of the CNS.[3] In addition, local therapies for parenchymal metastases, used increasingly in recent years, have been implicated in leptomeningeal seeding[7] and may lead to further increase in incidence.

Our survey did not confirm a rising incidence of CM overall but university hospitals and designated oncology centers observed an increase in the number of patients with CM secondary to breast cancer. The reason for that is hard to assess, although more frequent imaging in specialized centers may explain this discrepancy. Other possible explanations include an overall lower number of patients with MBC at general hospitals or private institutions, more advanced patients seeking care at academic centers, or longer survival of patients at academic centers and thus more patients at risk of developing CM.

Undoubtedly, optimizing diagnosis and treatment of CM represents an unmet need. The 2020 ESO-ESMO guidelines for advanced breast cancer address CM very briefly,[8] while the most recent ESMO guidelines do not mention CM directly, but refer to the previously issued edition.[9] The National Comprehensive Cancer Network (NCCN) and European Association of Neuro-Oncology (EANO)/ESMO[10,11] guidelines for CM management (officially referred to as leptomeningeal metastases in both guidelines) are not specific for breast cancer, although they do specifically recommend approaching CM according to the tumor of origin and suggest management decisions should be based on systemic disease burden and performance status. The recommendation is to diagnose the condition with CSF cytology whenever possible, use RT for areas that are symptomatic or block CSF flow, use systemic therapy as appropriate, and administer intrathecal methotrexate, preferably through an Ommaya catheter (NCCN), all with a very low (2A) level of evidence. A subgroup of the Response Assessment in Neuro-Oncology (RANO), named Leptomeningeal Disease Assessment In Neuro-Oncology (LANO), has been developing guidelines for the assessment of response to therapy in CM both for clinical trials and for clinical practice.[12]

Our survey found that most breast oncologists use MRI and/or CSF cytology to diagnose CM. It is unclear if lack of access to an MRI may have played a role in this for some

sites. Although current recommendations suggest that at least three CSF specimens should be obtained to rule out CM, in the case of neurological symptoms and negative CSF cytology, this practice is followed in very few of the sites participating in this survey. Similarly, only a few sites performed a CSF flow study before initiating therapy. These findings reflect the difficulties in implementing such a process within routine clinical practice, particularly as the procedures cause significant discomfort to the patient. Of note, the lack of effective therapy would likely be a deterrent to meticulous diagnostic pursuit. The use of circulating tumor DNA and tumor markers are being investigated as adjuncts to cytologic diagnosis. These techniques may eliminate the need for repeated spinal taps to confirm the presence of CM[13,14] and may lead to the identification of specific targetable mutations, unique to the CM clones, thus improving therapeutic options.[15] Interesting research is also conducted in the field of immunotherapy addressing the microenvironment of CM.[16]

So far, however, treatment of the condition has not seen any significant advances. This is reflected by the almost uniform use of methotrexate intrathecally despite its low response rates and lack of improvement of quality of life and patient-reported outcomes.[17] Interestingly, a very high percentage (58.1%) of sites do not use intrathecal therapy. Although we did not ask what is used instead of intrathecal therapy, it appears that RT is used in many of the sites. For example, in Asia where the rate for intrathecal therapy is quite low (27.6%), RT is used in 87.9% of sites. In retrospect we should have addressed the issue by including a specific question on why intrathecal therapy is not used and what is used in its place, but we did not anticipate this result. Systemic therapy is also attempted despite its limited efficacy.[18,19] Throughout our survey, in fact it has been impressive that despite the lack of guidelines with strong levels of evidence, the approach to patients with breast cancer with CM is similar globally, likely due to lack of alternative evidence-based treatment options. This further underlines the need for a registry to assess these uniformly adopted practices.

A somewhat surprising finding of our survey was the relative lack of a routine policy for referrals of patients with CM to palliative care. In many sites referral to palliative care is only allowed once tumor-directed therapy is discontinued, and this fact possibly explains the limited number of sites that refer all patients with CM for palliative care.

Palliative RT is used frequently, albeit not in all patients, for symptom control as recommended in most textbooks. Once again, the use of RT to the entire neuraxis is not used in most sites, also an area of almost uniform agreement, possibly because of the potential for significant toxicity in the setting of lacking evidence regarding its efficacy.[20]

Most sites expressed an interest in participating in a subtype-specific prospective study, although almost all described a concern regarding low accrual numbers. This highlights the importance of a large network such as BIG as the appropriate setting for such a trial as it has the number of academic breast cancer research groups and affiliated sites necessary to take on this endeavor in a rare disease entity. Studies are needed to assess all aspects of CM from breast cancer, that is, a registry for epidemiological purposes, including whether the therapies used to treat brain metastases affect the incidence of CM (e.g. increased incidence of CM after brain metastasectomy because of seeding), studies on diagnosis and CSF examination including circulating tumor DNA on CSF, and above all studies on therapy both intrathecal and systemic, always subtype-specific and mostly geared toward the subtypes more prone to CNS metastatic disease. Such studies should include pharmacokinetic proof of principle when systemic administration is used. The role of RT should be established in prospective studies as well. A framework with centers of expertise and dedicated multidisciplinary teams may be appropriate at a national or regional level.

A weakness of our survey is the fact that our questionnaire was not validated to make sure that the meaning of the questions was clear, and no important information was left out. In addition, there was a heavy bias for centers from the European countries because of BIG's predilection. Furthermore, because participation was on a voluntary basis, centers more interested in investigating and treating CM were more likely to answer the questionnaire, thus creating a bias in favor of the further study of this condition, while recall bias may have also affected the answers to the survey. Finally, we could have added more granularity to the questions, for example, asking how therapy decisions were affected by subtype or symptoms, but the analysis might have been complicated with open-ended questions. Having said that, when reviewing the answers that were given as free text under the section for comments, we feel that this work yielded a fairly accurate depiction of common practice for CM in BIG centers that responded to the questionnaire.

In conclusion, this first global investigation on the care of patients with CM from breast cancer demonstrates a high homogeneity between different parts of the world, and between different types of institutions with regard to diagnosis and treatment of CM. In addition, we could show that there is a high interest in conducting studies in this group of patients, who previously most often have been excluded from participation in prospective trials.

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