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Original article

Controversies in monitoring metastatic breast cancer during systemic treatment. Results of a GIM (Gruppo Italiano Mammella) survey

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ABSTRACT

Background: The optimal strategy for monitoring metastatic breast cancer (M-MBC) is unclear. Nevertheless, M-MBC influences patient's quality of life and it affects the use of resources in terms of both drugs and diagnostic exam prescription. We aim to disclose oncologists' approach on M-MBC, identifying controversial areas.

Methods: An anonymous online survey was conducted among GIM members who, based on their on-field experience, shared their own method for M-MBC planning. Chi-square tests and Fisher exact tests were used as appropriate.

Results: The survey was completed by 256 recipients (51%). The majority of them were medical oncologists. Approximately 50% of respondents reported that M-MBC was primarily based on the monitoring strategies used in clinical trials, and for 70% of them M-MBC should be evidence-based. Areas of controversies included the primary goal of M-MBC, the use of tumour markers, the optimal timing for baseline assessment and frequency of repeating testing. Respondents agreed on planning M-MBC before treatment's start and on discussing with the patient about the M-MBC strategy and on choosing CT-scan as the preferred reassessment imaging method. The most relevant factors influencing the M-MBC strategy were performance status, triple negative histology, exam's contraindication, the presence of clinically measurable disease, and treatment safety profile; on the contrary, patients' socio-economic status, exam's cost, and hospital's logistic limits were less relevant. Experienced oncologists seemed less prone to intensive follow-up.

Conclusion: M-MBC strategy still has controversial issues and its potential clinical effects for breast cancer patients need *ad hoc* studies.

1. Background

Thanks to advances in early detection and treatment, the death rate for female breast cancer (BC) dropped 38% from 1989 to 2014 [1]. Nevertheless, about 6% of women are de novo metastatic and about 30% of patients initially diagnosed with early stage disease will later develop metastatic breast cancer (MBC). Despite improvement in early breast cancer managing induced negative selection with adverse risk profiles of patients developing metastatic disease, worsened outcome was not confirmed, thanks to therapeutic improvements also in MBC [2–5]. Development of metastases in specific anatomic site was associated with clinico-

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pathological features, consistently with the complexity of MBC and its clinical manifestations [6,7].

Although treatment's selection is individualized, single agent sequential therapy (including targeted therapies, if required) is usually the preferred approach. Decisions for treatment duration and its selection in subsequent lines depend on the careful assessment of treatment response. Median progression free survival (PFS) varies according to therapy, tumour and patient characteristics [8].

Even if strategy and frequency of monitoring MBC (M-MBC) are primarily based on standardized methods utilized in breast clinical trials [9], when it comes to daily practice oncologists follow their patients by means of not necessarily standardized criteria. This leads to repeated imaging studies and clinical decision making (i.e. confirming or stopping the ongoing treatment) on the basis of both objective and symptomatic criteria [10,11].

Previous reports showed that more intense use of disease-monitoring tests was associated with higher total health care costs [12] while survival benefits of intensive M-MBC were uncertain. Also, emotional harms due to fear of disease progression and death have been reported by patients during monitoring of the disease outcome [13]. M-MBC influences first and foremost patient's life, furthermore it has a strong impact on use of resources in terms of both drugs and diagnostic exams. Nevertheless, optimal strategy of M-MBC has never been formally studied.

With the lack of strict recommendations from international guidelines, which are based on expert opinion derived from available guidelines and common clinical practice [14–16], the most appropriate strategy for M-MBC is perceived as one of the practice performance gaps in cancer care [17].

The aim of the present study was to disclose GIM (*Gruppo Italiano Mammella*) oncologists approach on M-MBC, identifying potential areas of controversy.

2. Methods

The analysis was conducted using an online survey addressed to GIM members. The GIM cooperative group represents the most important Italian network for clinical and translational research on BC, with more than 150 adherent centres and about 500 investigators involved. The study project was presented at the GIM national conference in September 2016. The survey was distributed between February and March 2017 in electronic form by using the online software *SurveyMonkey (SurveyMonkey Inc. San Mateo, California, USA.* www.surveymonkey.com). Three reminder emails were sent at different time points to encourage responses. It was allowed to skip questions that were judged not applicable. All responses were reported anonymously. The survey was administered in Italian language. The complete questionnaire was given in the Supplement S1 (in Italian language) and in the Supplement S2 (translated into English).

The first part of the survey was focused on the oncologists' opinion about role and objectives of M-MBC outside clinical trials. The second part was dedicated to the basal assessment (modality and timing). The third part addressed the physicians' own method and the importance of clinico-pathological features for M-MBC planning through a 0–100 scale, based on the on-field experience. The subsequent part, aimed to describe difference in M-MBC according to different settings through six simulated cases. The final questions gathered demographic and professional characteristics of respondents.

All the responses were compared according to characteristics of respondents, in order to identify difference of M-MBC approaches.

Quality control was implemented in several stages, from questionnaire design to consistency checks after the survey was completed.

All analyses were carried out using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Chi-square tests, and Fisher exact tests were used as appropriate after a comprehensive descriptive analysis.

3. Results

Two hundred and fifty-six recipients (51%) completed the survey. Characteristics of respondents are depicted in Table 1. Most of them were specialists (70%) and close to 50% of them had been involved in M-MBC for over 10 years as well as in Academic setting.

3.1. Perception of intensity and primary goal of M-MBC

As first question, respondents were asked to provide their own perception of M-MBC intensity, outside clinical trials. Responses are reported in Fig. 1. Strategies perceived as “intensive” M-MBC were CT-scan every 2 months, PET/CT-scans every 3 months, and bone scan every 3 months. On the other hand, CT-scan every 6 months and tumour markers (TM) every 3 months were defined as “not intensive” M-MBC.

To avoid toxicity or to detect disease progression (PD) earlier were frequently entered as the primary goals of M-MBC (59% and 41%, respectively). In the case of high-cost drugs, the possibility to avert unnecessary costs was identified as the primary goal of M-MBC by 34% of respondents (to avoid toxicity by 42% and to detect earlier PD by 24%).

For 36% of participants, M-MBC was based on clinical judgement, while 47% declared that strategies of M-MBC were based on standardized methods, similarly to those adopted in clinical trials. Interestingly particular, the most of the oncologists declared to define tumour response according to RECIST (Response Evaluation Criteria in Solid Tumours) guidelines while for 20% of them the decisions were based on clinical judgement.

Only 18% of respondents thought that strategies of M-MBC were defined by guidelines. For 70% of the oncologists decision about M-MBC should be evidence-based.

M-MBC was considered to influence quality of life with a median score of 69/100 and survival with a median score of 39/100.

All the responses were compared according to characteristics of respondents, in order to identify differences among M-MBC approaches. Statistically significant results are reported in Table 3a.

3.2. The basal assessment

Responses about baseline assessment are summarized in Fig. 2. Almost all of respondents declared to perform CT/MR scan (neither PET-CT nor RX/US). An additional brain CT/MR-scan was performed in all cases by 12% (27/233), in HER2-positive/triple negative (TN) cases by 51% (119/233), or in symptomatic patients by 80% (188/233) of respondents. Bone scan was ordered in presence of symptoms by 65% (152/233), in presence of bone metastases by 37% (87/233), and in any case only by 24% (57/233) of respondents. TM were dosed even if not elevated at diagnosis by 41% (96/232) of respondents, while only 4% (10/232) of them declared not dose TM at all. Almost the whole sample declared to reserve PET-CT for cases with equivocal conventional imaging results.

Differences according to characteristics of respondents are reported in Table 3b.

3.3. Assessment plan over the time

The minority (37/231) of respondents planned only the timing of first assessment, while 194 of them (84%) planned also further