Clinical Features and Prognostic Factors in Patients with Carcinomatous Meningitis Secondary to Breast Cancer

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Abstract: Prognosis in patients with carcinomatous meningitis (CM) is poor, and numerous prognostic factors for response and survival have been described, but remain controversial. In general, series are small and involve a heterogeneous type of solid neoplasms. The purpose of this study was to describe a series of patients with breast cancer-associated CM to determine the clinical features and prognostic factors associated with survival. We conducted a retrospective study on 49 patients diagnosed between January 2003 and December 2007 at the Instituto Nacional de Cancerología in Mexico City. CSF cytopathology samples were re-reviewed to confirm the diagnosis. Overall survival (OS) for patients with breast cancer with CM was 7 weeks. Factors independently associated with better OS included absence of encephalopathy at diagnosis (11 weeks versus 1 week; p = .036), low CSF protein content (15 versus 5 weeks; p = .022), and nontriple-negative receptor status in the primary breast cancer tumor (13 versus 3 weeks; p = .015). According to multivariate analysis, patients were divided into favorable and poor prognostic groups, with OS of 14 weeks and 2 weeks, respectively (p < .001). These factors can identify a subgroup of patients who are candidates for an intensive management approach.

Key Words: breast cancer, carcinomatous meningitis, leptomeningeal metastases, neoplastic meningitis, prognostic factors

Carcinomatous meningitis (CM), also known as leptomeningeal metastases or neoplastic meningitis, is a common oncologic complication representing spread of tumor cells to the subarachnoid space, which occurs in 4–7% of all patients with solid tumors (1,2). It is a complication that often portends a very short prognosis, as it is frequently associated with extensively disseminated and progressive systemic cancer. Small-cell lung cancer and melanoma have the highest rates of spread to the leptomeninges, at 11% and 23%, respectively (3,4). However, breast cancer accounts for the majority of cases in large series owing to its high incidence and its 5% risk of development of meningeal involvement (5,6).

Median survival time of untreated patients with CM is 4–8 weeks (7–9). However, the clinical course and neurological and systemic response may vary among patients with different neoplasms. Median survival time can be increased to 4–6 months in some selected cases treated with intensive approaches (10,11). Of the solid tumors, breast cancer has a median overall survival that ranges between 11 and 24 weeks (12–17). Three modalities of treatment have been used, including craniospinal irradiation, systemic chemotherapy, or local chemotherapy via lumbar puncture or intraventricular (Ommaya) reservoir. These have been used in combination or alone. However, the optimum treatment route and regimen have not been established, because the rarity of the complication has led to the publication of mostly small, heterogeneous and noncontrolled series. Furthermore, not all patients with CM are candidates for the aggressive treatment outlined previously (18), and should therefore receive palliative support.

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DOI: 10.1111/j.1524-4741.2012.01228.x

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The Breast Journal, Volume 18 Number 3, 2012 233–241
Several clinical factors have been investigated as survival predictors with the aim of identifying candidates for aggressive treatment, such as age, gender, duration of signs of CM, increased protein or low glucose in CSF, etc., but many remain controversial (6,19). This might be explained because the majority of reported series are undersized and include heterogeneous types of solid and hematologic malignancies, which might dilute the importance of the variables in study.

The search for factors predictive of survival might help the clinician choose which type of conduct to pursue specifically in breast cancer patients with CM. To determine a better selection of treatment strategies in these patients, the purpose of this study was to examine prognostic factors in breast cancer patients with CM that influence overall survival (OS) in order to predict which patients might warrant a more aggressive and definitive diagnostic and therapeutic approach.

PATIENTS AND METHODS

All patients with breast cancer and CM who were diagnosed and treated at the Instituto Nacional de Cancerología (National Cancerology Institute, INCan) in Mexico City between January 2003 and December 2007 were identified retrospectively. Patients with clinical or radiologic suspicion of CM but without cytological corroboration of malignant cells in CSF were excluded. All samples of positive CSF cytopathology were re-reviewed to confirm the diagnosis. Patients’ hospital records and office charts were reviewed. Demographics, pathological features of primary breast cancer, estrogen (ER), progesterone (PR) and human epidermal growth factor 2 (Her2) receptor status, stage at diagnosis, time from primary tumor diagnosis to onset of neurological symptoms and CM diagnosis, Karnofsky performance status, clinical presentation of CM, CSF biochemical parameters, treatment of CM, and time to death were analyzed.

Statistical Analysis

For descriptive purposes, continuous variables were summarized as arithmetic means, medians, and standard deviations (SDs), while categorical variables were expressed as proportions and confidence intervals. Inferential comparisons were carried out using the Student’s t-test or the Mann–Whitney U-test, according to data distribution determined by the Kolmogorov–Smirnov test. Chi-square or Fisher exact test was employed to assess significance among categorical variables. Statistically significant and borderline-significant variables (p < .1) were included in the multivariate logistic regression analysis.

Median OS was estimated in weeks and was calculated from date of diagnosis of CM until death or last follow-up. OS was analyzed with the Kaplan–Meier method, and comparisons among subgroups were performed with the log-rank test. For survival curve analysis, all variables were dichotomized. Adjustment for potential confounders was performed by multivariate regression analysis. According to regression coefficients, patients were classified as having good or poor prognosis for CM. Statistical significance was determined as p < .05 with a two-sided test. All statistical computations were performed utilizing the SPSS version 15.0 statistical software package (SPSS, Inc., Chicago, IL).

RESULTS

Patients’ Characteristics and Histologic Findings of Primary Disease

A total of 61 patients were diagnosed with CM between 2003 and 2007, of which 49 (80%) comprised cases related to primary breast cancer. Of the 49 patients, mean age of presentation was 42.4 years (range: 23–63 years) at the time of primary breast cancer diagnosis. Stage IV was documented in 25% of cases, and 92% of patients had nodal disease at initial diagnosis. Ductal carcinoma was identified in 76% of all cases, and high-grade histology comprised 47%. In nine patients the hormone and Her2 receptor status were unknown. Of the remaining 40 patients, 20% were ER positive, 27% PR positive, 20% Her2 positive, and 39% were triple-negative tumors. Mean number of chemotherapy schemes prior to progression to leptomeningeal disease was two. The clinical characteristics of the 49 patients at diagnosis of primary breast cancer are summarized in Table 1.

Presentation

Table 2 summarizes clinical presentation, CSF abnormalities, and imaging findings of patients with breast cancer at the time of diagnosis of CM. The median time from the first neurological symptoms to the confirmation of the diagnosis was 1.4 weeks (range: 0–6.3 weeks). Nearly one half of patients had...
a Karnofsky performance status of <70%. The most frequent sites of metastatic lesions were, in descending order, bone, brain, soft tissue, lung, and liver. One half of patients showed no evidence of macroscopic cerebral disease at time of CM diagnosis. Headache, nausea/vomiting, and paresia/paralysis were the initial symptoms in 67%, 43%, and 41% of cases, respectively. Twenty-five percent of patients presented with seizures and encephalopathy at diagnosis, respectively.

CSF Abnormalities and Imaging

The definitive diagnosis of CM was done by examination of the CSF obtained by lumbar puncture. Diagnosis of CM was confirmed cytologically by examination of Wright’s and papanicolaou stain using the Cytospin method. Forty-four patients were diagnosed after one lumbar puncture, three after two lumbar punctures, and two patients after >2 lumbar punctures. Mean nucleated cell count was 2.25 per high power field (HPF) (range: 0–23) and 12% of cases had abnormal CSF leukocytes >5/µL. Median CSF glucose was 53 mg/dL (range: 2–215 mg/dL), with 20% of patients with a CSF glucose level <40 mg/dL. Median CSF protein concentration was 63.5 mg/dL (range: 17–1,694 mg/dL) and 25% of cases were found to have an abnormal protein level >45 mg/dL.

Table 1. Patients’ characteristics and histologic findings at the time of treatment of primary breast cancer

| Characteristics | Number (%) |
|-----------------|------------|
| Age (years), mean (range) | 42.4 (23–63) |
| Stage | |
| I | 2 (4%) |
| II | 10 (21%) |
| III | 21 (51%) |
| IV | 12 (25%) |
| Nodal disease | 45 (92%) |
| Treatment | |
| Neoadjuvant chemotherapy | 34 (94%) |
| Chemotherapy schemes, mean (range) | 2 (0–6) |
| Grade | |
| Low | 3 (6%) |
| Intermediate | 10 (20%) |
| High | 23 (47%) |
| Unknown | 13 (27%) |
| Histologic subtypes | |
| Ductal | 37 (76%) |
| Lobular | 7 (14%) |
| Mixed | 2 (4%) |
| Undifferentiated | 1 (2%) |
| Paget | 1 (2%) |
| Unknown | 1 (2%) |
| Hormonal receptor status | |
| Estrogen-negative | 30 (61%) |
| Estrogen-positive | 10 (20%) |
| Unknown | 9 (18%) |
| Progesterone-negative | 27 (55%) |
| Progesterone-positive | 13 (27%) |
| Unknown | 9 (18%) |
| HER2 | |
| HER2-negative | 30 (61%) |
| HER2-positive | 10 (20%) |
| Unknown | 9 (18%) |
| Triple-negative cancer | |
| Yes | 19 (39%) |
| No | 21 (43%) |
| Unknown | 9 (18%) |

Table 2. Patients’ characteristics, CSF abnormalities, and imaging findings at time of diagnosis of carcinomatous meningitis

| Characteristics | Number (%) |
|-----------------|------------|
| Karnofsky performance status | |
| 90–100 | 3 (6%) |
| 70–80 | 24 (49%) |
| <70 | 22 (45%) |
| Systemic disease | |
| Absent | 8 (16.3%) |
| Controlled | 8 (16.3%) |
| Active | 33 (67.3%) |
| Loco-regional disease | |
| Controlled | 27 (55%) |
| Active | 22 (45%) |
| Metastatic site | |
| Bone | 25 (51%) |
| Central nervous system | 24 (49%) |
| Soft tissue | 19 (39%) |
| Lung | 13 (27%) |
| Liver | 13 (27%) |
| Nodes | 13 (27%) |
| Other | 13 (27%) |
| Symptoms and signs | |
| Headache | 33 (67%) |
| Nausea/vomiting | 21 (43%) |
| Paresia/paralysis | 20 (41%) |
| Lumbar pain | 14 (27%) |
| Encephalopathy | 12 (24.5%) |
| Seizures | 12 (24.5%) |
| Diplopia | 9 (18%) |
| Hypoesthesia | 8 (16%) |
| Nucal rigidity | 7 (14%) |
| Hydrocephalus (communicating) | 3 (6%) |
| Hydrocephalus (obstructive) | 1 (2%) |
| Number of lumbar punctures for diagnosis | |
| 1 | 44 (90%) |
| 2 | 3 (6%) |
| >2 | 2 (4%) |
| CSF | |
| Leukocytes (mean × HPF) | 2.25 (0–23) |
| Leukocytes >5/µL | 6 (12%) |
| Glucose (median, mg/dL) | 53 (2–215) |
| Glucose <40 mg/dL | 10 (20%) |
| Protein (median, mg/dL) | 63.5 (17–1,694) |
| Protein >45 mg/dL | 12 (25%) |
| MRI (brain and/or spinal column) | |
| Done | 33 (67%) |
| Positive for CM | 17 (51%) |

CSF, Cerebrospinal fluid; HPF, High power field; MRI, Magnetic resonance imaging; CM, Carcinomatous meningitis.
Thirty-three patients (67%) underwent magnetic resonance imaging (MRI) (brain and/or spinal column). The reason that one-third of the patients did not have a brain/spine MRI at CM diagnosis was that at the time this study was done at our Institute, the patients had to cover the expense of the imaging modalities by themselves, which limited the possibility of doing more expensive studies in some cases. These patients underwent an enhanced computed tomography (CT) of the brain and spine. In 51% of cases, abnormalities suggestive of CM were identified in MRI or contrast-CT. None of the patients underwent CSF flow studies. The CSF flow block was identified by evidence of hydrocephalus either by CT or MRI imaging.

**Survival**

Overall survival for patients with breast cancer with CM was 7 weeks (95% confidence interval [CI], 2.3–11.6 weeks) (Fig. 1). Univariate analysis revealed that factors associated with unfavorable prognosis were the following: age >42 years (p = .008); Karnofsky performance status <70 (p = .017); high-grade tumors (p = .017); negative progesterone receptor expression (p = .007); triple-negative breast cancer receptor status (p = .006), presence of encephalopathy (p = .001), occurrence of paresia/paralysis (p = .013), and high CSF protein content (0.002). The remaining variables that were studied by univariate analysis are reported in Table 3.

For OS, multivariate analysis yielded the following independent prognostic factors: absence of encephalopathy at diagnosis (11 versus 1 weeks; relative risk [RR], 2.5; 95% CI, 1.1–5.7; p = .036); low CSF protein content (15 versus 5 weeks; RR, 5.2; CI, 1.2–9.1; p = .022), and nontriple-negative receptor status in the primary breast cancer tumor (13 versus 6 weeks; RR, 2.4; CI, 1.1–3.7; p = .015).

### Table 3. Univariate and multivariate Cox regression analysis of prognostic indicators for carcinomatous meningitis

| Variable                        | Median weeks (95% CI) | p    | Relative risk | p     |
|---------------------------------|-----------------------|------|---------------|-------|
| Age (years)                     | 11 (4–18)             | .008 | 0.98 (0.5–2.0) | .969  |
| Karnofsky performance status    | ≥70 (8–16)            | .017 | 0.87 (0.4–1.5) | .267  |
| Grade                           | >70 (1–9)            | .017 | 3.0 (1.3–6.6)  | .070  |
| Hormonal receptors              | Positive              | 11 (0–23) | .078 |
| Estrogen receptors              | Positive              | 6 (0–15)  | .525 |
| HER2 receptors                  | Positive              | 18 (0–39) | .007 |
| Nontriple-negative breast cancer | ≥6 (2–10)            | .006 | 2.4 (1.1–3.7)  | .015  |
| Delay in diagnosis (interval in days between the onset of symptoms and initiation of treatment) | >14 (4–29) | .116 |
| Concomitant intracerebral metastases | Yes                  | 5 (0–13)  | .645 |
| Presence of encephalopathy      | Yes                   | 1 (0–3)   | .001 | 2.5 (1.1–5.7)  | .036  |
| Paresia/paralysis               | Yes                   | 5 (3–7)   | .013 | 0–92 (0.5–1.7) | .791  |
| Time from systemic progression to diagnosis of CM (months) | >12 (5–10) | .528 |
| Leukocytes in CSF               | ≤5/μL                 | 11 (6–16) | .250 |
| Glucose in CSF                  | ≤40 mg/dL             | 3 (0–9)   | .122 |
| Protein in CSF                  | ≥45 mg/dL             | 15 (8–22) | .002 | 5.2 (1.2–9.1)  | .022  |

95% CI, 95% Confidence interval; CM, Carcinomatous meningitis. Bold values are those statistically significant.
3 weeks; RR, 2.4; CI, 1.1–3.7; p = .015) (See Table 3 and Fig. 2). In Figure 3, the OS of CM patients presenting one of these negative prognostic factors (favorable prognostic group) is compared against those with two or three factors (poor prognostic group). According to multivariate analysis, patients with favorable and poor prognosis had an OS of 14 and 2 weeks, respectively (p < .001). Neither presence of metastatic brain lesions nor identification of carcinomatosis in imaging studies represented prognostic factors for survival.

Treatment

Once the diagnosis was established, the patient’s overall status was assessed to determine how aggressively the patient should be treated. According to NCCN guidelines, patients were stratified patients into “poor risk” and “good risk” based on Karnofsky performance status, degree of neurologic deficits, extent of systemic disease, and available treatment options (20,21). Patients with good risk included those with a KPS of 60 or above, absence of or modest fixed neurologic deficits, minimal disease burden, or systemic cancer for which there were reasonable treatment options. For these individuals, more aggressive measures were considered, such as intrathecal therapy, radiotherapy to bulky or symptomatic areas of leptomeningeal disease, and optimal systemic treatment for the extraneural disease component.

Treatments that patients received are presented in Table 4. Twenty-nine patients (59%) were treated with intrathecal methotrexate with a mean of four
applications. The administered dose was 15 mg every week until neurologic symptoms resolved or improved or up to a cumulative intrathecal dose of 150 mg. The Ommaya reservoir was utilized in 16% of patients.

A follow-up negative CSF was documented in 13 patients (45%), and mean number of cycles required to obtain negative CSF was three. Patients who were treated with intrathecal methotrexate (29 patients) had a longer survival than those who were offered only supportive measures or radiotherapy (20 patients) (14 versus 2 weeks; p < .0001), as shown in Figure 4. There were no reported cases of acute or delayed leukoencephalopathy.

Twenty-two patients (45%) received systemic chemotherapy after diagnosis of CM, and one patient received four lines of chemotherapy. Patients with HER2 positive disease did not receive treatment with trastuzumab. This was because it was not until 2006 that the government covered for trastuzumab therapy. None of these patients were managed with hormonal or targeted therapy. Cranial radiotherapy (30 to 36 Gy in 10 to 12 daily fractions) was administered to 51% of patients owing to symptomatic and/or bulky disease. Fourteen percent of patients received treatment to the entire neuroaxis because of CSF flow block before the administration of intrathecal therapy or multifocal neuraxis involvement.

## DISCUSSION

In this study, of the 61 patients diagnosed with CM, 49 (80%) had a primary breast cancer diagnosis. Although breast cancer is not the main cancer with leptomeningeal dissemination, it is the most frequent malignant tumor reported in the majority of series (7,8,22). Commonly, CM presents in patients with active and progressive systemic disease in up to 70% of cases (23,24), which is similar to the 67% reported in this study.

The most common presenting feature was headache, reported in 67% of cases, similar to other series that describe a frequency that varies between 32% and 75% (25). Nuchal rigidity was present in 14% of cases, according to other studies that report a low frequency, which approximates 15% (7,8,26–28). Hydrocephalus was diagnosed in 8% of patients (communicating in 3 patients and obstructive in one). Hydrocephalus may occur due to ependymal nodules or tumor deposits obstructing CSF-outflow channels, particularly at the level of the fourth ventricle or basal cisterns. Communicating hydrocephalus has been reported in 7–16% in other series(7,29) and obstructive hydrocephalus has been seen in 2% of cases of patients with neoplastic meningitis(7).

It is important to notice that only 51% of MRI studies showed abnormalities considered diagnostic of CM. It has been reported that MRI with gadolinium enhancement has a false negative rate that exceeds 30%, so a normal study does not exclude the diagnosis of CM (18).

Treatment for CM is given at our Institution with intrathecal methotrexate at a dose of 15 mg every week until neurologic symptoms resolve or improve (despite CNS cytology results), or is administered for 15 mg every week up to a cumulative intrathecal dose.
of 150 mg when the clinical neurologic course does not recover or worsens, for a total of 10 weeks. In patients with resolution or improvement of symptoms, intrathecal methotrexate is reinitiated at the same previous dose if neurological function deteriorates.

We have chosen to guide our management by the clinical manifestations, instead of the conversion from positive to negative cytology. Other authors have considered that the neurologic status appears to be a better predicting factor for further survival compared with the cytologic response after the first 6 weeks of intensive treatment (13) and given that CSF cytology reflects only the response to treatment of free-floating cells, some authors found that neurological status may be a better predictor of treatment efficacy (30). We opted to administer the intrathecal methotrexate weekly, similar as the consolidation phase of the standard recommended treatment (31), because in this way the time to reach the maximum dose of methotrexate is prolonged. Neurological complications of intrathecal treatment have been reported in some series in almost half of the treated patients, and delayed leukoencephalopathy is not a rare complication of intrathecal methotrexate therapy (17). It has been shown that its incidence is related to the cumulative dose of methotrexate, the duration of treatment, and its combination with whole brain irradiation (32). Delayed leukoencephalopathy has been reported in patients receiving cumulative doses of 150–170 mg MTX without whole brain radiotherapy (17), and with even lower doses if treatment is combined with radiation (32). With our treatment approach, none of the patients in our cohort treated with intrathecal methotrexate developed acute or delayed leukoencephalopathy. Similarly, Nakagawa et al. reported no cases of leukoencephalopathy in patients with CM treated with single low-dose intrathecal methotrexate (5 mg) alone or combined with cytosine arabinoside (33).

Several prognostic markers have been examined, but many remain controversial. However, it is generally accepted that patients will do poorly if any of the following variables are present at the moment of delivery of intensive treatment of CM: poor performance status (22), multiple fixed neurologic deficits (13), bulky CNS disease (34), co-existent carcinomatous encephalopathy (35), CSF flow abnormalities (36, 37), and widely metastatic aggressive cancers that do not respond well to systemic chemotherapies (13).

We found that the presence of encephalopathy at the time of diagnosis represents an adverse independent prognostic factor. Patients with encephalopathy (that included delirium and altered state of consciousness) had an OS of 1 week versus 11 weeks in patients without this clinical manifestation. Chamberlain et al. compared two cohorts of 20 patients, each of whom was diagnosed with CM with and without encephalopathy, with a median OS of 10 weeks in the cohort with CM-related encephalopathy compared with 24 weeks in the cohort without CM-related encephalopathy (p < .001) (35).

Patients with a normal CSF protein content, which indicates the absence of widespread leakage through diseased meninges, had a longer median survival (12). Other authors have reported a worse prognosis in patients with CM and elevated CSF protein levels (7, 13). However, other reports have not confirmed this association (38, 39). The conflicting results from these studies may be owing to differences in the primary malignancies studied, sizes of the study groups, and variables examined.

Triple-negative breast cancer patients comprised 39% of the total population, and had a worse prognosis than the nontriple-negative counterparts (13 versus 3 weeks; p = .015). Triple negative breast cancer confers a poor prognosis and has a predilection for visceral metastasis, including lung, liver and, notably, brain metastasis. Current estimates are that approximately 15% of TNBC patients develop brain metastasis (40, 41). The risk for developing brain metastasis is higher for patients with TNBC than with other types of breast cancer (42–44). Studies have shown that even in patients with cerebral metastasis, TNBC patients have a poor prognosis, as metastasis to the brain occurred earlier and have a shorter median survival following a diagnosis of brain metastases than other breast tumor subtypes (43, 44). In our series, we found a high prevalence of triple-negative breast cancer patients with CM who had a worse prognosis than their nontriple-negative counterparts.

To the best of our knowledge, this is the first study that reports that the absence of expression of progesterone receptors in the primary breast cancer as a poor prognostic factor. Boogerd et al. (45) described two patients with breast cancer-related leptomeningeal metastases who were treated with hormonal therapy, which provided a neurologic response of at least 12 months and a survival of 14 and 19 months, which may be associated with the fact that hormone
receptor-positive tumors are often less aggressive than those in patients with hormone receptor-negative tumors.

Our study presents several limitations. Its retrospective nature did not permit evaluation of a standard diagnostic or therapeutic approach. Moreover, other important prognostic factors described previously were not confirmed in this study, perhaps owing to the limited number of patients, to demonstrate a significant difference.

Overall survival of patients was 7 weeks, which agrees with previously reported data if patients are left untreated (8,14). Patients who were treated with intrathecal chemotherapy survived for 14 weeks compared with those who received palliative radiotherapy or supportive care, which suggests that intrathecal chemotherapy may improve the outcome of these patients, as described in other reports (15,38,46). It is possible that this more favorable outcome reflects a better performance status or a better general condition of the patients who received intrathecal treatment, secondary to simply a selection bias. Hence, the exact value of intraventricular and systemic therapy in patients with MC still has to be determined.

The Karnofsky status was not a prognostic factor associated with poor outcome in this report. We believe that patients without systemic contraindications to receive chemotherapy should be considered for intrathecal management, even if they have a poor performance condition, given that this presentation might be secondary to the CM itself.

The main contribution of these findings is that all patients included in this study were cases with breast cancer corroborated by CSF cytology and that one new prognostic factor was described. In conclusion, prognosis of patients with breast cancer with CM is poor. However, patients with absence of encephalopathy at diagnosis, low protein CSF content, and nontriple-negative receptor status in primary breast cancer tumor are favorable prognostic factors associated with longer OS in patients with breast cancer with CM. These factors can identify a subgroup of patients who are candidates for an intensive management approach.

Acknowledgments

Study conception and design: Lara-Medina, Arrieta; Follow-up and management of patients: Lara-Medina, Gamboa-Vignolle; Surgical treatment: Ruiz-González; Collection of data: Crismatt, González-Pinedo; Cytopathology revision: Flores-Hernández; Analysis and interpretation of data: Villarreal-Garza, Arrieta; Systematic review of literature and drafting of manuscript: Crismatt, Villarreal-Garza, Arrieta; Final approval of manuscript: Lara-Medina, Crismatt, Alvarado-Miranda, Villarreal-Garza, Flores-Hernández, González-Pinedo, Gamboa-Vignolle, Ruiz-González, Arrieta.

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