Chemical meningitis related to intra-CSF liposomal cytarabine

Bénédicte Durand^{1,2}, Fahed Zairi^{1,3,4}, Thomas Boulanger⁵, Jacques Bonnetterre^{1,2}, Laurent Mortier^{1,6} & Emilie Le Rhun^{*,1,2,3,4}

¹Lille University, F-59000 Lille, France

²Oscar Lambret Center, Medical Oncology Department, F-59000 Lille, France

³Inserm, U-1192, F-59000 Lille, France

⁴CHU Lille, Neurosurgery Department, F-59000Lille, France

⁵Oscar Lambret Center, Department of Radiology, F-59000 Lille, France

⁶CHU Lille, Dermatology Department, F-59000Lille, France

* Author for correspondence: Tel.: +33 3 20 29 59 43; Fax: +33 3 20 29 59 34; e-lerhun@o-lambret.fr

Therapeutic options of leptomeningeal metastases include intra-cerebrospinal fluid (CSF) chemotherapy. Among intra-CSF agents, liposomal cytarabine has advantages but can induce specific toxicities. A *BRAF*-V600E-mutated melanoma leptomeningeal metastases patient, treated by dabrafenib and liposomal cytarabine, presented after the first injection of liposomal cytarabine with hyperthermia and headaches. Despite sterile CSF/blood analyses, extended intravenous antibiotics were given and the second injection was delayed. The diagnosis of chemical meningitis was finally made. Dose reduction and appropriate symptomatic treatment permitted the administration of 15 injections of liposomal cytarabine combined with dabrafenib. A confirmation of the diagnosis of chemical meningitis is essential in order (1) not to delay intra-CSF or systemic chemotherapy or (2) to limit the administration of unnecessary but potentially toxic antibiotics.

First draft submitted: 1 December 2016; Accepted for publication: 3 May 2017; Published online: 23 October 2017

Keywords: leptomeningeal metastasis • neoplastic meningitis • toxicity

Practice points

- Bacterial and chemical meningitis can share the same clinical presentation, with headache, neck stiffness, fever, nausea/vomiting and altered general status.
- In the presence of symptoms of meningitis occurring after an intra-cerebrospinal fluid (CSF) injection of liposomal cytarabine, direct bacterial analysis and culture of the CSF should always be performed.
- When bacterial meningitis is suspected, empiric antibiotics should be started as soon as possible until the results of CSF culture analysis become available.
- To decrease the risk of chemical meningitis, steroid prophylaxis should start the day before the injection of intra-CSF liposomal cytarabine and be maintained for a total of 5 days.
- The management of chemical meningitis may include high dose of steroids, in association with further symptomatic treatments such as antiemetic drugs and analgesics.
- The dose of intra-CSF liposomal cytarabine should be reduced for further injections in case of chemical meningitis uncontrolled by symptomatic treatments.

Leptomeningeal metastases (LM) are diagnosed in 5–10% of patients with solid tumors [1]. The incidence of LM may increase in the coming years because of a prolonged control of extracerebral disease and because of the use of antineoplastic agents with a poor coverage of the CNS [2]. Breast cancer, lung cancer and melanoma are the most common primary solid cancers causing LM [1]. The diagnosis is based on the identification of cancer cells in the cerebrospinal fluid (CSF), or in the absence of cancer cells in the CSF, on neurological symptoms and signs in presence of compatible neuroradiological findings, consistent radiographic criteria on MRI of the craniocervical axis [2–8].

The median overall survival of untreated LM patients varies from 4 to 6 weeks [9,10], whereas the median overall survival of treated patients varies from 3.3 to 6 months in breast cancer [2,4,11–15], from 2 to 4.3 months in lung cancer [6,16–19] and from 2.5 to 3.8 months in melanoma [8,20,21]. LM can be responsible of various fixed and severe neurological deficits that negatively impact patients' quality of life [22]. Thus, the prognosis of LM remains poor despite combined therapeutic approaches.

Although no randomized study has proven its efficacy, intra-CSF chemotherapy is often used concomitantly with systemic drugs to bypass the blood–CSF barrier when the systemic agents have only a poor CNS penetration. Limits of intra-CSF chemotherapy include a limited penetration into nodular meningeal nodules and CSF flow blocks. This must be taken into account when therapeutic options are discussed [2].

The main drugs currently used for the intra-CSF treatment are (liposomal) cytarabine, methotrexate and thiopeta. Since the results of the trial of Glantz *et al.*, liposomal cytarabine is frequently chosen as first-line intra-CSF treatment because of a similar efficacy in terms of overall survival but a significantly improved progression-free survival and a better quality of life as compared with methotrexate [23]. The long half-life of liposomal cytarabine, in comparison to the other agents, necessitates fewer visits to the hospital and wider intervals between injections (one dose every 2 weeks for 2 months followed by one dose every 4 weeks in case of response or stabilization). Due to the limited tolerability of the sustained release formulation, this agent requires the administration of oral steroid prophylaxis for 5 days after the intrathecal injection for the prevention of chemical meningitis.

The present case study highlights the importance to diagnose chemical meningitis in the perspective of avoiding potentially detrimentally delayed or discontinued systemic and intra-CSF treatments and maintaining neurological function and quality of life of patients.

Description of the case

A 49-year-old male was treated in our institution for metastatic melanoma with *BRAF* (V600E) mutation. His medical history began in 2008, when a left axillary melanoma (Breslow 1.84 mm, Clark IV) was surgically removed. In 2011, diffuse metastases involving lymph nodes, lung, liver, adrenal gland and brain (asymptomatic single right anterior parietal lesion) were diagnosed. The patient maintained a good general status with a WHO performance status of 0. He received dabrafenib from August 2011 to November 2013. The response was initially good with disease stabilization and the patient kept a performance status of 0. In October 2013, asymptomatic progression of the previously described single right parietal brain metastasis was observed, whereas the extra-CNS disease was stable. In early November 2013, this lesion was surgically removed, without any complication. Dabrafenib was stopped at the time of the surgery.

In December 2013, the patient complained of headaches and neck stiffness. Brain and spinal MRI identified new left periventricular and left medial temporal lesions. The biochemical analysis of the CSF revealed increased protein (0.91 g/l), decreased glucose (0.50 g/l) and increased leukocytes (21/mm³). The cytological analysis showed malignant cells in the CSF confirming the diagnosis of LM. After multidisciplinary discussion, dabrafenib was restarted in association with intra-CSF liposomal cytarabine.

The first dose of cytarabine (50 mg) was injected by lumbar route. Prednisolone was already administered by infusion at 80 mg per day for the management of neurological symptoms and was continued from the first day of injection for a total duration of 5 days and then reduced. The next day, the patient was admitted for a 38.5°C fever and an alteration of the general condition. The brain CT scan did not disclose any new abnormality. The analysis of the CSF revealed a low rate of glucose (0.04 g/l), an elevated level of protein (2.54 g/l) and an increased level of leukocytes (11,920/mm³). The blood analysis revealed a minor inflammatory syndrome (increased CRP at 31 g/l and leukocytosis of 12,500/mm³). Direct bacteriological analysis and PCR for *Neisseria meningitidis* and *Streptococcus pneumoniae* were negative. A diagnosis of bacterial meningitis was suspected and intravenous antibiotics including cefotaxime, fosfomycin and metronidazole, then cefotaxime and linezolid, were initiated. Although the CSF culture remained negative and no germ was identified, the treating physician decided to administer antibiotics for 3 weeks. Dabrafenib, which has no hematological toxicity, was maintained but intrathecal chemotherapy was suspended until the end of the antibiotics. Steroids were stopped a few days after admission by the treating physician. The fever disappeared after the first infusion of antibiotic treatment and the general condition quickly improved after symptomatic treatment. The diagnosis of chemical meningitis was then proposed as all the symptoms were consistent with a fever linked to a side effect of the liposomal cytarabine.

Intra-CSF liposomal cytarabine was restarted again at a reduced dose, 25 mg was administered for the second injection, performed 27 days after the first injection rather than 14 days. Treatment with prednisolone 120 mg

Figure 1. Coronal gadolinium enhanced MRI at diagnosis (left) and after 1 year (right) of treatment with dabrafenib and intra-cerebrospinal fluid liposomal cytarabine.

on the day of injection and 80 mg for the next 5 days was instituted. No adverse reaction was reported after this second injection.

For the third intrathecal injection, a full dose of 50 mg of liposomal cytarabine was administered in association with oral steroids and antiemetics. 2 days later, the patient presented with fever and stiff neck (headache and nausea). Since the symptoms were compatible with chemical meningitis and as he already presented with the same symptoms after the first intrathecal injection, no antibiotic was initiated and the symptoms disappeared on intravenous prednisolone 100 mg after 1 day. Direct bacterial analysis and CSF cultures remained negative. A ventricular device was implanted after exclusion of active infection. From the fourth injection, the dose was kept at 25 mg of liposomal cytarabine, and high dose of oral prednisolone (80 mg) and ondansetron (8 mg) was maintained for 5 days from the first day of administration.

A total of 15 injections of liposomal cytarabine were given for a whole year combined with dabrafenib. No tumor cells in the CSF were identified from the time of the third intra-CSF injection, before the implantation of the ventricular device. Brain and spine MRI showed a reduction of the volume of the left periventricular and medial temporal lesions after 1 year of treatment.

The patient was still alive 1 year after the end of administration of the intra-CSF treatment, and monitored by regular physical examinations, MRIs and lumbar punctures (Figure 1). He kept a good quality of life, authorizing him to pursue his high social and work-related position at 36 months after diagnosis.

Discussion

Intra-CSF injections may cause complications that can be due to procedures of injection or directly to the chemical agent injected.

Complications due to procedures may vary according to the way of drug administration into the CSF. Complications related to the lumbar route include local pain at the injection site, extra-subarachnoid distribution of the intra-CSF drugs and infections [24]. Infections such as bacterial meningitis remain rare and because they can usually be avoided using strict hygienic measures. Usual precautions related to lumbar puncture in general are required (adequate platelet count, no exposure to anticoagulants, absence of brain mass effect).

The ventricular route is often chosen because of its advantages in term of pain and in drug distribution throughout the neuraxis [25]. One randomized trial has also suggested a survival benefit in terms of progression-free survival when methotrexate was given by the intraventricular route [26]. Moreover, this route can be used with a lower platelet count (20,000 cells/mm³ or greater). This improves compliance and comfort of patients but is also more time efficient for the physician. However, in a cohort of 112 consecutive patients treated with intra-CSF treatment, with a median number of 9.34 injections per patient and combined with systemic agents in 72% of the cases, an overall complication rate of 9.8% after the implantation of a ventricular access device has been reported [27]. Complications include local infection (6.2%), leukoencephalopathy, hemorrhage or misplaced or disconnected catheter. In a previous study of 120 adult patients treated with a total of 520 cycles of liposomal cytarabine, bacterial meningitis was reported in 3.75% of the injections but only with intraventricular administration [28]. Thus, the indication of the surgery for placement of an intraventricular device should be weight against the general status of the patient.

Complications due to drug administration include headaches, nausea, vomiting but also neck stiffness and fever, and may vary by the drug administered [28]. Acute toxicities reported with methotrexate are aseptic meningitis, sensory or motor dysfunction, acute encephalopathy and subacute transverse myelopathy [23,29]. Aseptic meningitis of Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4 has been reported in 3% of methotrexate cycles despite dexamethasone use [23]. Late toxicities were reported as soon as 1988, with the report of a disseminated necrotizing leukoencephalopathy on 9 out of 14 patients treated by intrathecal methotrexate. This toxicity is much more frequent when methotrexate is combined to whole-brain radiotherapy [30].

With use of intraventricular thiotepa, fewer neurological toxicities have been reported [31].

The main adverse event of liposomal cytarabine is chemical meningitis, which is slightly more frequent after cytarabine injection than after methotrexate injection and is reported in 15–23% of cycles (including 5% of CTCAE grade 3–4) when dexamethasone were added versus 19% including 3% of grade 3–4 with methotrexate [23,28]. The frequency of chemical meningitis raised up to 60% after liposomal cytarabine in the absence of steroid prophylaxis [23]. Symptoms usually reported as chemical meningitis include headaches, nausea and vomiting, and are more likely to appear on the first injection [28,32]. Other toxicities related to cytarabine include fatigue, cognitive impairment, communicating hydrocephalus, conus medullaris/cauda equina syndrome, decreased visual acuity, leukoencephalopathy, myelopathy, radiculopathy and seizures [28,33].

As seen in this case report, chemical meningitis may be severe and lead to hospitalizations and delay in treatments. To decrease the risk of chemical meningitis, steroid prophylaxis should start the day before the injection and be maintained for a total of 5 days. Symptoms can be managed by the use of higher dose of dexamethasone or methylprednisolone, in association with further symptomatic treatments [28]. Personalized prophylaxis medications include antiemetics or analgesics when necessary. The duration of intra-CSF injection should be performed over 1–5 min as recommended by the legal notice. Dose reduction may be an option when these measures are not sufficient. However, in a retrospective cohort of 103 patients treated with liposomal cytarabine as first-line treatment of LM, no dose reduction was reported [34].

The initial presentation of bacterial and chemical meningitis may be similar in some points. The diagnosis of bacterial meningitis is urgent, because treatment should be initiated as soon as possible. However, it is important to confirm as soon as possible the final diagnosis, in order to avoid delays in administration of tumor-specific therapies and to avoid long unnecessary treatments in frail patients.

In both cases, patients can present headaches, neck stiffness, fever and nausea/vomiting in patients with an altered general status. These symptoms usually trigger a lumbar puncture. Bacterial or chemical meningitis can present with identical CSF findings, including increased leukocyte counts, and decreased glucose. At LM diagnosis, protein CSF concentrations (>50 mg/dl) are increased in 76%, decreased glucose (<50 mg/dl) are observed in 54% and increased leukocytes (>4/mm³) in 46% of the cases [2].

Liposomal cytarabine particles may be mistaken for leukocytes because of their aspect and size, thus it must be specified to the laboratory when a patient is treated with liposomal cytarabine [35]. In bacterial meningitis, increased CSF protein and decreased CSF glucose values can be observed, too. The most important criterion for the diagnosis of infectious meningitis is the identification of bacteria at direct examination or at culture and the detection of bacterial antigens by latex agglutination or identification of bacterial genome by multiplex polymerase chain reaction [36]. Serum parameters, such as serum C-reactive protein, serum procalcitonin may also been taken into account but are of limited value [36].

At least, a potential impact of the combination with dabrafenib on the tolerance of intra-CSF chemotherapy cannot be excluded and could be explored in prospective cohorts.

The physiopathology of chemical meningitis induced by intra-CSF liposomal cytarabine remains poorly understood at the molecular level. However, as symptoms were observed within 24 h after injection of liposomal cytarabine and resolved after steroid administration, an inflammatory mechanism may be assumed.

The long-term survival in our patient is also noteworthy, since median survival for LM from melanoma remains very limited. No clear recommendation exists for the treatment of these patients. A poor penetrance of the blood–brain barrier and high interindividual variability in BRAF inhibitor diffusion into CSF should be considered [37]. A recent study reported on long-term survival of patients with LM from melanoma treated by targeted therapeutics, including dabrafenib, or immune checkpoint inhibitors [8]. In this study, the median survival for patients for which treatment included a BRAF inhibitor was 24.9 versus 2.9 weeks by patients who did not receive any therapy.

Conclusion & future perspective

The differential diagnosis between infectious and chemical aseptic meningitis is important in this population of frail patients. In case of suspicion of infectious meningitis, a CSF sample should be collected for the bacterial analysis and intravenous antibiotics should immediately be started. The identification of a bacteria in the CSF is of importance. Establishing the diagnosis of chemical meningitis permits to avoid potential delays in intra-CSF chemotherapy and systemic treatments that could lead to worsening of the neurological status and institution of palliative care and potential toxic prolonged antibiotics treatments. This case illustrates this importance of the differential diagnosis between infectious and chemical aseptic meningitis in the population of patients treated with intra-CSF liposomal cytarabine.

Financial & competing interests disclosure

Le Rhun has received research support from Mundipharma and Amgen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

References

Papers of special note have been highlighted as: • of interest

- 1 Clarke JL, Perez HR, Jacks LM *et al.* Leptomeningeal metastases in the MRI era. *Neurology* 74(18), 1449–1454 (2010).
- 2 Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumors. *Surg. Neurol. Int.* 4(Suppl. 4), S265–S288 (2013).
- 3 Brem SS, Bierman PJ, Brem H *et al.* Central nervous system cancers. *J. Natl Compr. Cancer Netw.* 9(4), 352–400 (2011).
- 4 Gauthier H, Guillaume MN, Bidard FC *et al.* Survival of breast cancer patients with meningeal carcinomatosis. *Ann. Oncol.* 21(11), 2183–2187 (2010).
- 5 Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. *Med. Oncol.* 30(1), 408 (2013).
- 6 Kuiper JL, Hendriks LE, van der Wekken AJ *et al.* Treatment and survival of patients with EGFR-mutated non-small cell lung cancer and leptomeningeal metastasis: a retrospective cohort analysis. *Lung Cancer Amst. Neth.* 89(3), 255–261 (2015).
- 7 Scott BJ, Oberheim-Bush NA, Kesari S. Leptomeningeal metastasis in breast cancer – a systematic review. *Oncotarget* 7(4), 3740–3747 (2015).
- 8 Geukes Foppen MH, Brandsma D, Blank CU *et al.* Targeted treatment and immunotherapy in leptomeningeal metastases from melanoma. *Ann. Oncol.* 27(6), 1138–1142 (2016).
- 9 Chamberlain MC, Glantz M, Groves MD *et al.* Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. *Semin. Oncol.* 36, S35–S45 (2009).
- 10 Groves MD. New strategies in the management of leptomeningeal metastases. *Arch. Neurol.* 7(3), 305–312 (2010).
- 11 Grossman SA, Trump DL, Chen DCP *et al.* Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. *Am. J. Med.* 73(5), 641–647 (1982).

- 12 DeAngelis LM. Current diagnosis and treatment of leptomeningeal metastasis. *J. Neurooncol.* 38(2–3), 245–252 (1998).
- 13 Rudnicka H, Niwińska A, Murawska M. Breast cancer leptomeningeal metastasis – the role of multimodality treatment. *J. Neurooncol.* 84(1), 57–62 (2007).
- 14 Clatot F, Philippin-Lauridant G, Ouvrier M-J *et al.* Clinical improvement and survival in breast cancer leptomeningeal metastasis correlate with the cytologic response to intrathecal chemotherapy. *J. Neurooncol.* 95(3), 421–426 (2009).
- 15 de Azevedo CRAS, Cruz MRS, Chinen LTD *et al.* Meningeal carcinomatosis in breast cancer: prognostic factors and outcome. *J. Neurooncol.* 104(2), 565–572 (2011).
- 16 Morris PG, Reiner AS, Szenberg OR *et al.* Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. *J. Thorac. Oncol.* 7(2), 382–385 (2012).
- 17 Park JH, Kim YJ, Lee J-O *et al.* Clinical outcomes of leptomeningeal metastasis in patients with non-small cell lung cancer in the modern chemotherapy era. *Lung Cancer* 76(3), 387–392 (2012).
- 18 Gwak H-S, Joo J, Kim S *et al.* Analysis of treatment outcomes of intraventricular chemotherapy in 105 patients for leptomeningeal carcinomatosis from non-small-cell lung cancer. *J. Thorac. Oncol.* 8(5), 599–605 (2013).
- 19 Lee SJ, Lee J-I, Nam D-H *et al.* Leptomeningeal carcinomatosis in non-small-cell lung cancer patients: impact on survival and correlated prognostic factors. *J. Thorac. Oncol.* 8(2), 185–191 (2013).
- 20 Harstad L, Hess KR, Groves MD. Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. *Neuro-Oncol.* 10(6), 1010–1018 (2008).
- 21 Pape E, Desmedt E, Zairi F *et al.* Leptomeningeal metastasis in melanoma: a prospective clinical study of nine patients. *Vivo Athens Greece* 26(6), 1079–1086 (2012).
- 22 Jaeckle KA. Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment. *Semin. Oncol.* 33(3), 312–323 (2006).
- 23 Glantz MJ, Jaeckle KA, Chamberlain MC *et al.* A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. *Clin. Cancer Res.* 5(11), 3394–3402 (1999).
- **This is one of the few randomized trials in the field, indicating activity of intrathecal DepoCyt in neoplastic meningitis from solid tumors.**
- 24 Mack F, Baumert BG, Schäfer N *et al.* Therapy of leptomeningeal metastasis in solid tumors. *Cancer Treat. Rev.* 43, 83–91 (2016).
- 25 Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. *N. Engl. J. Med.* 293(4), 161–166 (1975).
- 26 Glantz MJ, Van Horn A, Fisher R *et al.* Route of intracerebrospinal fluid chemotherapy administration and efficacy of therapy in neoplastic meningitis. *Cancer* 116(8), 1947–1952 (2010).
- 27 Zairi F, Le Rhun E, Bertrand N *et al.* Complications related to the use of an intraventricular access device for the treatment of leptomeningeal metastases from solid tumor: a single centre experience in 112 patients. *J. Neurooncol.* 124(2), 317–323 (2015).
- **This is an interesting and large series of complications associated with intraventricular chemotherapy for neoplastic meningitis.**
- 28 Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. *J. Neurooncol.* 109(1), 143–148 (2012).
- **This is an interesting and large series of complications associated with intraventricular chemotherapy for neoplastic meningitis.**
- 29 Ackermann R, Semmler A, Maurer GD *et al.* Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites. *J. Neurooncol.* 97(3), 425–427 (2009).
- 30 Boogerd W, vd Sande JJ, Mofie D. Acute fever and delayed leukoencephalopathy following low dose intraventricular methotrexate. *J. Neurol. Neurosurg. Psychiatry* 51(10), 1277–1283 (1988).
- 31 Grossman SA, Finkelstein DM, Ruckdeschel JC *et al.* Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 11(3), 561–569 (1993).
- 32 Jaeckle KA, Batchelor T, O'Day SJ *et al.* An open label trial of sustained-release cytarabine (DepoCyt) for the intrathecal treatment of solid tumor neoplastic meningitis. *J. Neurooncol.* 57(3), 231–239 (2002).
- **This is an early experience highlighting the potential use of DepoCyt in solid tumor-derived neoplastic meningitis.**
- 33 Boogerd W, van den Bent MJ, Koehler PJ *et al.* The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study. *Eur. J. Cancer* 40(18), 2726–2733 (2004).
- 34 Le Rhun E, Taillibert S, Zairi F *et al.* A retrospective case series of 103 consecutive patients with leptomeningeal metastasis and breast cancer. *J. Neurooncol.* 113(1), 83–92 (2013).
- 35 Strik H. Cell count and staining. In: *Cerebrospinal Fluid in Clinical Neurology*. Deisenhammer F, Sellebjerg F, Teunissen CE *et al.* (Eds). Springer, Basel, Switzerland, 81–100 (2015).
- 36 Viallon A, Botelho-Nevers E, Zeni F. Clinical decision rules for acute bacterial meningitis: current insights. *Open Access Emerg. Med.* 8, 7–16 (2016).

- **Provides guidance on the management of bacterial meningitis.**

37 Sakji-Dupré L, Le Rhun E, Templier C *et al.* Cerebrospinal fluid concentrations of vemurafenib in patients treated for brain metastatic *BRAF*-V600 mutated melanoma. *Melanoma Res.* 25(4), 302–305 (2015).