Management of Adult Patients Receiving Intraventricular Chemotherapy for the Treatment of Leptomeningeal Metastasis

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Cancer in the central nervous system can arise from a primary brain tumor and metastasize to the brain or to the leptomeninges, leading to leptomeningeal metastasis (LM). LM also is called leptomeningeal carcinomatosis and carcinomatous meningitis. When LM occurs, signs and symptoms include headache, nausea, vomiting, lumbar back pain, and stiff or painful neck; LM also may lead to mental disturbances and seizures. Nursing care of patients with LM requires an understanding of neurologic anatomy and physiology, along with associated treatments and complications. Treatment of LM may involve intrathecal or, more likely, intraventricular chemotherapy. Very little has been written about appropriate care of patients with LM. The purpose of this article is to review the literature, summarize clinical care recommendations, and construct evidence-based guidelines for the administration of intraventricular chemotherapy and the care and monitoring of patients with LM.

At a Glance

Leptomeningeal metastasis is a complex condition with multiple neurologic sequelae. It occurs primarily with leukemia and lymphoma but also is associated with solid tumor cancers.

Treatment of leptomeningeal metastasis often involves intrathecal or intraventricular chemotherapy.

Use of evidence-based guidelines for the care and management of patients receiving intraventricular chemotherapy will promote safe use of the infrequent treatment.

A 42-year-old man with AIDS and B-cell lymphoma was admitted to the inpatient mixed medical-surgical-oncology unit. He had been treated as an outpatient. He presented with severe lumbar back pain, right-eye ptosis, lower-extremity weakness, and anal “numbness.” The physician performed a lumbar puncture (LP) but could not collect enough fluid, so a second LP was performed. Multiple diagnostic tests were run; the patient’s pain worsened, as did his lower-extremity weakness. He eventually required an indwelling catheter for urinary incontinence. Five to seven days later, leptomeningeal metastasis (LM) was confirmed. An intraventricular (IVt) reservoir (e.g., Ommaya port) was placed, and chemotherapy (CTX) agent cytarabine was administered.

Staff required substantial guidance regarding assessment and management of the patient, particularly regarding his IVt CTX. This is a type of IT administration, which also can be given via LP. The institution had no policies for nursing care of patients receiving IVt CTX, pharmacy preparation of IVt CTX, or proper administration techniques.

The patient received CTX through the IVt port for one cycle. His lumbar pain worsened, and his neurologic status deteriorated. He exhibited symptoms of cauda equina syndrome, characterized by dull pain in the lower back and upper buttocks along with lack of feeling in the buttocks, genital area, and upper thighs. Bowel and bladder function often are impaired by LM, caused by nerve impairment in the spinal root nerves. He began spinal radiation but died within the week. Unfortunately, the man spent his last month of life in the hospital, in pain, with worsening neurologic status.

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Leptomeningeal Metastasis

LM can occur from the spread of leukemia, lymphoma, or a solid tumor such as breast, lung, gastrointestinal tract, or brain (Demopoulos & Posner, 2006a). Primary central nervous system lymphoma is an aggressive form of non-Hodgkin lymphoma that arises in the brain, eyes, leptomeninges, or spinal cord and often involves LM (Abrey, Yahalom, & DeAngelis, 2000). Approximately 5%–20% of patients with metastatic cancer develop LM (Chamberlain, Kormanik, & Barba, 1997). LM is increasing in frequency, with an overall incidence as high as 8% in patients with cancer (Belford, 2004).

The leptomeninges are two tissue linings that cover the brain and spinal cord. The layers, the arachnoid and the pia mater, encase the arachnoid space, which contains cerebrospinal fluid (CSF) (see Figure 1). Tumor cells can invade the CSF through multiple entry points, which include brain parenchyma, blood vessels, metastasis to the choroid plexus, extension from spinal metastasis, invasion along peripheral or cranial nerves, or directly from the meninges. When cancer metastasizes to the leptomeninges, it is LM, also known as meningeal carcinomatosis. Once cancer has spread to the CSF, it spreads throughout the entire neuraxis (Berg & Chamberlain, 2003), defined as “the axial unpaired part of the central nervous system, composed of the spinal cord, rhombencephalon, mesencephalon, and diencephalon” (American Heritage Stedman’s Medical Dictionary, n.d.). Because LM usually occurs with advanced disease, prognosis after diagnosis and treatment is usually less than six months. Without treatment, survival may be as short as four weeks. LM can occur in patients without evidence of systemic disease. In such cases, prognosis averages 12 weeks (Gordon & Myers, 2003). Treatment options for LM are limited but include IT CTX, systemic CTX that is usually high dose, palliative radiation, corticosteroids, and pain management (Lassman et al., 2006).

Presenting symptoms of LM are neurologic in nature and can indicate the location of pathology. Headache, nausea, vomiting, and mental status changes indicate cerebral hemisphere involvement. Cranial nerve involvement usually is exhibited as diplopia, facial weakness, hearing loss, and dysphagia. Spinal cord or nerve root involvement leads to back pain, radiculopathy, myelopathy, or paraparesis (Berg & Chamberlain, 2003). Transverse myelopathy is less common and presents as isolated spinal cord dysfunction; it may occur in patients receiving concurrent IT methotrexate and radiation. With myelopathy, patients can develop back pain, leg pain, paraplegia, sensory loss, and sphincter dysfunction (Wen & Plotkin, 2006). Other symptoms at LM presentation may include increased intracranial pressure, nuchal rigidity, dizziness, “numb chin syndrome,” radicular pain, incontinence or retention, hydrocephalus, and encephalopathy (Berg & Chamberlain; Demopoulos & Posner, 2006a; Gordon & Myers, 2003). Patients with LM often demonstrate cognitive changes such as altered mental status and confusion. Transient ischemic attacks and strokes also may develop if the vasculature of the brain is compromised (Gordon & Myers).

Until the cause of symptoms is established, patients may require multiple diagnostic tests, including cranial imaging, gadolinium-enhanced magnetic resonance imaging (MRI with contrast), CSF cytology by LP, and CSF flow studies (Gordon & Myers, 2003). Because an LP can cause spot enhancement on an MRI, MRI should be obtained prior to any procedure involving LP. Unfortunately, cytology specimens may not be conclusive, leading to repetitive LPs for diagnostic confirmation. Because of low sensitivity, cytology is negative in 20% of patients with LM (Demopoulos & Posner, 2006a). Even with negative imaging and negative CSF cytology, if a patient with cancer exhibits multiple neurologic symptoms, a diagnosis of LM often is assumed (Berg & Chamberlain, 2003).

Treatment

Systemic CTX, IT or IVt CTX, cranial and spinal radiation, and corticosteroids are the mainstays of medical management.
Because a typical LM prognosis is six months, the focus of LM treatment is palliative (Berg & Chamberlain, 2003; Demopoulos & Posner, 2006b). For patients with multiple comorbidities and poor performance status, supportive services may be provided without treatment. Because of LM diffuseness, treatment involves the entire neuraxis (brain and spinal cord) (Berg & Chamberlain). People with increased intracranial pressure may need shunt placement and are not candidates for CTX (Sandberg, Bilsky, Souweidane, Bzdil, & Gutin, 2000).

Radiation provides symptom relief more quickly than CTX. It may be given concurrently with CTX (IT or systemic). External beam radiation can be delivered to the entire neuraxis, to symptomatic sites, or to sites with bulky disease (Demopoulos & Posner, 2006b). For patients with bilateral lower-extremity weakness, the lumbosacral area can be irradiated. Major side effects of radiation for LM are myelosuppression, mucositis, esophagitis, and leukoencephalopathy, a condition affecting the brain’s white matter. Leukoencephalopathy is more likely when patients receive concurrent CTX (IT or systemic), particularly methotrexate. Patients who have received central nervous system CTX followed by brain radiation are at risk for late neurotoxicities, which occur months after completion of therapy (DeAngelis, 2001).

Chemotherapeutic agents typically used for LM include methotrexate and cytarabine. Monoclonal antibodies and biologic agents are under investigation for such use. Vinca alkaloids (e.g., vincristine) are never administered into CSF because they can cause paralysis or death.

IT CTX can be given via LP; however, because patients with LM often have had multiple invasions into the spinal fluid, this is not the desired method of treatment. LP access can lead to leakage of CTX into the epidural space or surrounding tissue (Berg & Chamberlain, 2003), pain from repeated LPs, difficulty with repeated insertion because of scar tissue formation, and unreliable drug concentrations in the ventricles of the brain. To avoid such complications, an ITV approach is preferred. A ventricular reservoir (e.g., Ommaya) is surgically placed under the skin of the scalp into the ventricle of the brain. This provides continuous access to the CSF, ensuring drug delivery.

Unfortunately, current literature regarding care of patients with LM predominately relates to medical management. No published guidelines are available on the clinical monitoring of patients with LM. Guidelines on IT administration for pain medications exist (Camp-Sorrell, 2004) but none specific to IT CTX. Safety guidelines were developed in the United Kingdom following several fatal errors with IT administration of vinca alkaloids (Health Services Council, 2003), but the recommendations do not direct nursing care.

**Nursing Care of Patients Receiving Intraventricular Chemotherapy**

**Preprocedural Patient Assessment**

Oncology nurses play a key role in the care of patients with LM. Primarily, care involves education and support. Patients and families need to understand what is happening, why patients may be confused, and the treatments and types of procedures involved in treatment. They need information to make informed decisions about how to proceed with a diagnosis of LM.

Before administration of IVt CTX, patients must be made comfortable. This involves toileting and administration of appropriate pain medications. Although specific premedications are not required for the procedure, patients may benefit from anti-anxiety medications. Some patients also require an antiemetic. Nurses should complete and document a neurologic assessment prior to administration of IVt CTX (Sandberg et al., 2000).

**Drug Preparation and Administration**

IT and IVt CTX agents must be prepared in a pharmacy, under a biologic safety cabinet, and in sterile conditions. Sterile, preservative-free saline should be used to decrease neurotoxicity (Berg & Chamberlain, 2003). When preservatives have been used, some patients have experienced transient paresis (Dunkelman, Earl, & Twelves, 1991).

Definitive guidelines on preparation of IT and IVt CTX syringes do not exist. An informal survey of nurses indicates that some facilities place the sterile syringe in a sterile bag under a biologic safety cabinet, then affix the drug label to the outside of the bag, which becomes the unsterile surface. In that procedure, a label is not placed on the syringe itself, which remains sterile. Other facilities prepare the syringe under sterile conditions and affix an unsterile label on the syringe, making the syringe unsterile.


- **Prepare IT or IVt medication in the pharmacy as close to administration time as possible, then deliver the drug to a separate designated area (separate from other CTX medications).**
- **Wrap IT or IVt drugs in a sterile bag, then wrap again in a sterile towel or another bag labeled “FOR INTRATHECAL USE ONLY.”** Wraps or packages should be removed immediately prior to administration by the person administering the drug.
- **Prior to the start of CTX administration (an invasive procedure), conduct a final verification to confirm correct patient, procedure, site, and availability of appropriate documents. Verification uses active—not passive—communication techniques.**

The 2006 National Patient Safety Goals included a new requirement: Label all medications, medication containers (e.g., syringes, medicine cups, basins), and other solutions on and off the sterile field in perioperative and other procedural settings (“JCAHO Announces 2006 Patient Safety Goals for Ambulatory Care Facilities,” 2005).

IT or IVt CTX typically is administered by an oncologist. In some states, specially trained nurses can obtain privileges to administer such medications (Camp-Sorrell, 2004). Providers should always wear sterile gloves, a gown, and mask during administration.

**Preparation of Equipment and the Sterile Field**

Prior to the actual administration of IVt CTX, all equipment should be gathered and a sterile field prepared. Staff and fam-
ily should be instructed not to disturb providers while CTX is being administered because it is crucial to patient safety that the medications are delivered correctly via the right route and because the risk of meningitis is increased when people without masks are in the room. Those involved should wear masks that cover the nose and mouth; this decreases the risk of transfer of *Streptococcus salivarius* to the treatment field (Baer, 2000; Laurila, Kostamovaara, & Alahuhta, 1998; Schneebberger, Jansen, & Voss, 1996).

Preparing the skin prior to accessing the Ommaya reservoir is a controversial topic. Based on animal studies from the 1950s–1980s indicating neurotoxicity from the use of chlorhexidine, the U.S. Food and Drug Administration (FDA) has required a label warning stating, “Avoid contact with meninges.” However, the American Society of Regional Anesthesia and Pain Medicine’s 2006 guidelines recommend that alcohol-based chlorhexidine should be considered the antiseptic of choice before regional anesthesia procedures, which is epidural, performed by LP. Based on at least one randomized, controlled trial, chlorhexidine solutions significantly reduced the likelihood of catheter and site colonization. This does not address IVT site preparation (Hebl, 2006). Therefore, following the FDA’s warning seems the most prudent practice. 10 percent povidone-iodine is the current recommendation for IVT and IT chemotherapy administration.

Figure 2 offers a recommended standardized procedure for accessing an IVT reservoir and administering CTX (Blaney & Poplack, 1996; Camp-Sorrell, 2004; Demopoulos & Posner, 2006b).

### Patient Safety

IT and IVT CTX errors related to the wrong drug or wrong route have been reported (Health Services Council, 2003). Vincristine is a vesicant intended for IV administration. It has been inadvertently confused with central nervous system CTX. When vincristine is given IT or IVT, it is fatal. Errors may be caused by mislabeling, mixed-up syringes, or failure to label syringes (Health Services Council). Figure 3 lists recommendations that can contribute to patient safety with IT or IVT CTX.

### Complications and Monitoring

Patients who have received IT or IVT CTX have had their CSF tapped. As with any patient who has received an LP, they should be encouraged to drink fluids to replenish CSF and decrease the chance of headache (Franges, 1996). Because reports suggest that iatrogenic meningitis may occur following access to the CSF (Johnson & Sexton, 2006), face masks are recommended during procedures that access CSF, especially if procedures may be prolonged or during instillation or removal of fluids such as with CTX administration (Baer, 2000; Franges).

Potential adverse results of a ventricular reservoir include infection, catheter malposition, and intracranial hemorrhage (Sandberg et al., 2000). The most common complications from IVT CTX include aseptic meningitis (inflammation of the lining of the brain [meninges] where bacteria do not grow in cultures of the cerebrospinal fluid) and myelosuppression (Chamberlain et al., 1997). In fact, aseptic meningitis can affect 10% of patients. Presenting symptoms may include headache, nuchal rigidity, back pain, nausea and vomiting, fever, and lethargy. Corticosteroids administered either orally or with IT CTX may decrease the incidence of aseptic meningitis.

Cognitive complications related to IT or IVT CTX administration include reversible posterior leukoencephalopathy syndrome (see Figure 4), confusion, hallucinations, delusions, transient aphasia depression, suicidal ideation and behavior, irritability, and changes in mental status. Patients with a psychiatric history are more likely to develop psychiatric symptoms. If symptoms are not reversed, patients can develop permanent dementia or go into a persistent vegetative state (Wen & Plotkin, 2000; Franges).

Figure 2. Procedure for Accessing an Intraventricular Reservoir for Chemotherapy Administration

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>As with all chemotherapy (CTX) administration, patient is informed and consent is signed. If substantial mental status changes exist, a guardian or person with power of attorney must provide consent.</td>
</tr>
<tr>
<td>2.</td>
<td>Initial assessment of patient’s vital signs and neurologic status is documented.</td>
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<tr>
<td>3.</td>
<td>The patient is made comfortable; he or she can be supine, semirecumbent, or seated; the patient’s head should be supported on a pillow.</td>
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<tr>
<td>4.</td>
<td>Instillation is a sterile procedure, so a sterile field is prepared and maintained.</td>
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<tr>
<td>5.</td>
<td>A healthcare professional palpates the reservoir by gently depressing, leaving fingers in place. The reservoir will fill with cerebrospinal fluid (CSF).</td>
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<td>6.</td>
<td>The intraventricular reservoir is cleansed with alcohol swabsticks and 10% povidone-iodine; allow betadine to dry for 30 seconds.</td>
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<tr>
<td>7.</td>
<td>25-gauge or smaller noncoring butterfly needle or scalp vein needle with extension tubing attached is inserted into the reservoir at a 45° angle.</td>
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<tr>
<td>8.</td>
<td>Two syringes are needed for the procedure: one to withdraw CSF, one with CTX medication to be infused. The withdrawal syringe size can be the same as the medication syringe size because the amount of CSF fluid withdrawn will be equivalent to the amount of CTX infused.</td>
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<tr>
<td>9.</td>
<td>Attach the empty syringe to the extension tubing and allow CSF to flow freely into the syringe.</td>
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<tr>
<td>10.</td>
<td>Slowly withdraw CSF (equaling volume to be infused) over two to five minutes. Reserve 2–3 ml to use as a flush after the drug is instilled. Any CSF remaining in the syringe can be sent for cytology.</td>
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<tr>
<td>11.</td>
<td>The syringe containing the drug should be at room temperature to prevent headache.</td>
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<tr>
<td>12.</td>
<td>Administer CTX slowly over two to three minutes (approximately 2 ml per minute). This can be slowed if the patient experiences headache.</td>
</tr>
<tr>
<td>13.</td>
<td>The remaining CSF is injected into the reservoir over two to three minutes (or 2 ml per minute); intermittently aspirate to ensure placement.</td>
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<tr>
<td>14.</td>
<td>The needle is removed from the reservoir, and light pressure is applied with a sterile 4 x 4 gauze pad.</td>
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<tr>
<td>15.</td>
<td>Gently pump the reservoir three to five times to assist in distribution of drug. The patient may hear the sound of the fluid filling the reservoir. The patient also may experience headache, nausea, or dizziness.</td>
</tr>
<tr>
<td>16.</td>
<td>Patient remains supine or semirecumbent for 30 minutes after procedure is completed.</td>
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</table>
IT cytarabine can cause chemical arachnoiditis, headaches, encephalopathy, transient paraplegia and seizures, transverse myelitis, and, rarely, aseptic meningitis. Liposomal cytarabine, a sustained-release cytarabine, may be used; the agent maintains a therapeutic drug level in the CSF for as long as 28 days (Demopoulos & Posner, 2006b).

In rare circumstances, high doses of systemic cytarabine can cause acute cerebellar syndrome, characterized by somnolence, encephalopathy, and ataxia and often beginning two to five days after treatment (Blaney & Poplack, 1996). Onset of acute cerebellar syndrome indicates toxicity and may resolve in some patients. Cytarabine treatment must be stopped immediately.

IT interferon has been studied to treat LM, brain tumors, and progressive multifocal leukoencephalopathy. Neurologic symptoms such as headache, vomiting, fever, and nausea can occur within hours of initial treatment. Encephalopathic symptoms can develop within several days. Again, cranial irradiation tends to worsen the symptoms (Wen & Plotkin, 2006).
General
1. Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine, and any new vinca drugs) are for IV use ONLY and are NOT to be injected into the cerebrospinal fluid. All vinca alkaloid syringes and bags must be labeled with drug information. They also must be clearly labeled “FOR IV USE ONLY.”
2. Only physicians and specially trained nurses can administer intrathecal (IT) or intraventricular (IVt) chemotherapy (CTX).
3. When IT or IVt CTX is to be given, nurses use standard CTX checks (e.g., signed consent, dosage double-checks, and pre-administration laboratory values such as white blood cell counts). A comprehensive baseline neurologic examination is performed and documented.
4. Syringes containing chemotherapeutic agents MUST be labeled with the drug information and its intended use (e.g., IT or IVt).
5. Access to the IT or IVt space is sterile. The syringe containing the drug does not need to be sterile. If the facility prefers to use a sterile syringe, a sterile label must be used. Syringes containing IT CTX must have a label clearly stating the drug, dosage, and its use. For example, “FOR INTRATHECAL USE ONLY.” Negative labeling such as “NOT FOR INTRAVENOUS USE” should not be used.
6. Cerebrospinal fluid (CSF) CTX should be administered during hours when all specialty personnel required are available.
7. Institutional policies should cover IT and IVt administration of CTX.
8. IT and IVt drugs should be administered at a separate time than IV drugs. IV drugs should be administered first. This eliminates the risk of giving an IV drug via the IT route.
9. IT and IVt chemotherapies are stored separately from IV CTX in the pharmacy and in medication rooms.
10. Staff members should wear face masks during procedures that involve accessing CSF (e.g., lumbar puncture, use of Ommaya reservoirs).

Preparation
1. IT/IVt CTX is prepared under a biologic safety cabinet hood in the pharmacy.
2. Sterile, preservative-free saline is used.
   a. After the syringe is prepared, an unsterile label is placed on the syringe with the patient name, drug name, dose, route, and administration time.
   b. Another label that reads, “FOR INTRATHECAL USE ONLY” provides additional protection from medication errors.

Administration
1. Accurate placement of a new IVt reservoir must be confirmed using a computed tomography scan.
2. Patients and families need clear preprocedural instructions. Preprocedural care includes emptying the bladder and bowel if possible, administering appropriate analgesics and antiemetics, gathering baseline vital signs, and performing a comprehensive neurologic assessment.
3. Medication orders and consent are checked, as with any chemotherapeutic agent.
4. An appropriate work environment is prepared, including necessary equipment.
5. A sign is placed outside the room (e.g., “DO NOT DISTURB. PROCEDURE IN PROGRESS”).
6. The patient is positioned supine for procedure.
7. Standard personal protective equipment for CTX administration must be used. The person administering the CTX must wear a gown, double gloves, and face mask. A sterile field is set up and maintained.
8. A “time-out” must be performed immediately prior to administration to verify that the correct medication is being administered using the correct dosage to the correct patient.
9. Prepare the site with alcohol swabsticks and 10% povidone-iodine.
10. CSF is removed slowly (~ 2 ml per minute) prior to instillation of CTX. The volume removed will equal the volume to be administered to minimize neurologic sequelae of the procedure. Care is taken to avoid air embolism into the CSF.
11. The IT or IVt CTX is administered slowly (~ 2 ml per minute).
12. CSF aspirate can be used to flush CTX from tubing.
13. If normal saline is used as a final flush, it must be preservative free.
14. After the procedure is complete, the nurse holds gentle pressure to the Ommaya site with gauze. The patient’s head is elevated as tolerated by the patient.
15. After administration, the equipment is disposed in a chemotherapeutic waste container.
16. A vacutainer is NEVER used to withdraw CSF; rapid withdrawal of fluid could damage the choroid plexus of the ventricle.
17. During the procedure, the nurse monitors the patient, performing frequent neurologic checks (before, immediately after, twice every two hours, every four hours for 24 hours, then every eight hours throughout care). Vital signs are assessed concurrent with neurologic checks.
18. Complications are monitored, such as hypertension and fluid overload and local reservoir site and systemic infection.

Case Study Revisited
Care of the patient could have been handled differently. With more knowledge of the low likelihood of cure of LM, staff would have been stronger advocates for the patient in palliation of symptoms, rather than active treatment. The patient would have had more in-depth counseling, and attention to his psychosocial needs in the terminal phase of his care would have been preeminent. Administration of IVt CTX would have been according to the guidelines in Figure 5. Oncology nursing needs to continue to develop the evidence related to this patient population. The population is a low-volume, high-risk group. Errors related to care can be fatal. Safety features must be included in all care, and patients’ short-term prognoses should be taken into consideration.

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