

## **Coping with 8H9 Intrathecal Antibodies**

### **Part 1: Background**

Memorial Sloan-Kettering Cancer Center (MSKCC) has developed a protocol using the “intrathecal 8H9 antibody” to treat neuroblastoma relapses in the brain and central nervous system (CNS). Parents whose children have undergone the 8H9 treatment report that it is generally well-tolerated by patients. In fact, many feel that the primary “coping” involved, rather than any difficult side effects for the patient, is becoming familiar with another new treatment, and one that may seem more invasive than traditional chemotherapy or radiation. The focus of this chapter is to better acquaint families with the unique features of the 8H9 treatment, its particular terminology, procedures and schedules.

The information provided in this chapter is from families who have gone through the treatment and from the sources listed at the end of this chapter; however, it is not intended as a substitute for guidance from your medical team. As always, families and patients must rely on their medical team as the best source of information about any NB treatment and its relevance for the specific patient, and the only source of medical advice.

### **Part 2: 8H9 Treatment Protocol**

#### **Overview of the Intrathecal 8H9 Antibody Treatment**

The intrathecal 8H9 antibody treatment is one part of a multi-modal protocol that also uses surgery, chemotherapy (regular and high-dose), cranio-spinal irradiation and 3F8 immunotherapy (systemic, not intrathecal) to treat neuroblastoma relapses in the brain and CNS. This protocol was developed at MSKCC and has been in use since 2003. As of 2012, MSKCC is the only medical institution in the world administering the 8H9 antibody.

8H9 is an antibody designed in the laboratory to target and attach to a certain molecule on an NB cell. Although 8H9 is similar to the 3F8 antibody, it targets a different molecule from the one that attracts 3F8 to an NB cell. The 8H9 antibody is “radiolabeled,” meaning that it has a type of liquid radiation attached, which it can deliver to NB cells that remain in the CNS after the surgery, chemotherapy and radiation therapies. The 8H9 targets only the NB cells, and not the normal brain tissue. In certain cases, 131-I-3F8 therapy is used intrathecally for CNS neuroblastoma recurrences and is a decision made with your MSKCC care team.

The term “intrathecal” refers to the space between the thin layers of tissue that cover the brain and spinal cord, which is filled with a fluid known as the cerebrospinal fluid (CSF). During the treatment, the 8H9 antibody is injected directly into this fluid through an “omaya reservoir” placed in the patient’s head for this purpose.

Since the use of the omaya reservoir is a new experience for almost all families of patients starting the 8H9 treatment, we have provided more information about it below.

## The Ommaya Reservoir

### Placement:

The ommaya reservoir is a port placed under the scalp on the top of the patient's head (either left or right side is possible). The catheter of the ommaya is threaded into a ventricle in the brain to provide access to the CSF for treatment and testing. The ommaya is placed by a neurosurgeon, and the procedure may be done at the time of tumor removal or prior to the start of 8H9 therapy as a different surgery. Note, however, that if the ommaya reservoir is placed later on in the treatment process, the timing of the procedure can sometimes be complicated to plan, due to the impact of chemotherapy, count recovery and other factors.

If the ommaya is placed in a separate procedure, it typically requires a post-surgical overnight hospital stay. The patient may require pain medication to help deal with the discomfort of the ommaya placement surgery. The procedure is usually tolerated very well, with minimal discomfort for only a few hours after the surgery. Because the ommaya protrudes above the skull it looks like a little bump, but it usually isn't noticeable when the patient has hair. Ommaya reservoirs require no maintenance and do not need to be cleaned or flushed.

### Accessing the Ommaya:

When the ommaya reservoir is accessed, a sterile field is first created. The skin on top of the ommaya is cleaned very carefully with iodine, and a thin needle with tubing attached is inserted through the scalp and into the ommaya (in a very similar manner to accessing a port). You will often hear this referred to as an "ommaya tap". A syringe is then attached to the tubing to push medication in or to draw CSF samples out.

Although accessing the ommaya reservoir is generally painless, many patients don't enjoy the process. Just the idea of a needle going into one's head can create anxiety for some, especially young children. Placing an EMLA, or topical numbing cream, on the ommaya prior to it being accessed may help patients who don't like the sensation; however, others may find that this additional step creates even more stress. You'll likely identify your own coping and distraction strategies (e.g., playing a game on a hand-held device, watching a movie, reading a book, etc.) to help reduce any anxiety your child may experience during a tap.

Ommaya taps occur during the 8H9 treatment and are also done during routine check-ups after the completion of 8H9. When the ommaya is accessed in a post-treatment exam, the process lasts only a few minutes. The taps are done by either the doctor or nurse practitioner. The skin over top of the ommaya is cleaned with iodine, the needle is inserted, the CSF sample is taken, and the needle is withdrawn. It is possible that the patient may feel a little tired and dizzy after an ommaya tap; however, this should be only a transient side effect. If the process of the ommaya tap causes the patient a great deal of stress, it may be possible to arrange for the tap to be done while the patient is sedated for a scan or other procedure.

Since there is a risk of an infection at the site of the ommaya whenever it is placed, accessed, and/or removed, the decision may be made with the family's approval simply to leave the ommaya in the patient permanently after treatment, and remove it only if any sort of risk or problem arises, which is very rare. Removing an ommaya can also disrupt the scar tissue, causing possible hemorrhage or

seizures where this risk did not previously exist. The decision to keep or remove the ommaya reservoir can be discussed with your medical team.

### **Summary of MSKCC's CNS Relapse Protocol**

The following is a brief summary of the CNS relapse protocol utilized by MSKCC (as of 2012). There may be variations on a case by case basis or at any point in time during the treatment phases. Your medical team will give you a copy of the protocol and explain it to you. However, we are summarizing it here to help you better know what to expect, and to include a few practical insights from families of patients who have been treated on the protocol. The various steps in the protocol are listed below in general order of their usual occurrence.

#### 1. Tumour Removal

- It is possible the ommaya reservoir will be placed at this time, as discussed above.

#### 2. Cranio-Spinal Irradiation

- The patient receives approximately 17 (or possibly more) rounds of radiation to the head and spine, often with a boost of radiation at the location of the tumor.
- As with cranial radiation during frontline treatment, a mesh “mask” is made for the patient to help hold his/her head and shoulders in place when the radiation is given. For each radiation session, the mask is placed over top of the patient’s face and fastened to the table to ensure that he/she remains in the proper position. Young children may need to be sedated for the planning and radiation sessions, as determined with your medical team on a case by case basis. There is information available from the Child Life team that can help introduce a child to what will be involved during radiation treatment. Parents might also explore whether it is possible for their child to be introduced to this procedure in advance by a play therapist.
- The patient may also receive 5 days of irinotecan chemotherapy during radiation. The purpose of the irinotecan is to help sensitize the neuroblastoma cells to the radiation.

#### 3. High-Dose Chemotherapy

- The patient receives temozolomide and irinotecan in high doses for 5 days. Generally, the dosing is greater than front-line chemotherapy but somewhat less than stem-cell transplant. If the patient has residual systemic disease, carboplatin may also be added to the first 2 days of this chemotherapy treatment. In some cases, the medical team and parents may decide that the benefit of this chemo is outweighed by the potential for significant (and possibly additional) hearing loss in the specific patient’s case.
- Approximately 72 hours after the last dose of chemotherapy, the patient may receive a stem cell rescue to help with count recovery. If banked stem cells are not available, it may take longer for counts to recover after this course of chemotherapy. The decision to use or not use banked stem cells is another important decision to be discussed with your medical team.
- 24 hours after stem cell rescue, or sooner, G-CSF is started. Blood counts should be done every 2-3 days and kidney and liver tests done weekly, or even more frequently if there are any concerns.
- In-patient admissions for fevers and neutropenia can be expected after this high-dose chemotherapy, as well as platelet and blood transfusions.

For more information on coping with chemotherapy, see Chapter 3, **—Coping with Treatment: Side Effects, Comfort, and Safety—Getting Through Chemotherapy.**

#### 4. Scans and Tests

- The full battery of scans and tests are done before starting the 8H9 therapy to ensure that the patient does not have any new or growing disease. According to protocol, all scans and tests must be done within 3 weeks of the start of 8H9. If any scans are outside of this timeline, they must be repeated. Counts must also be within certain ranges.
  - Prior to the first dose of 8H9, the ommaya reservoir is tapped, and a CSF sample is taken for study purposes and to test for micrometastatic neuroblastoma cells. A CSF flow study using DTPA (111-Indium diethylene triamine pentaacetic acid) is also done to confirm the good working condition and position of the ommaya reservoir. DTPA is injected through the reservoir and a nuclear medicine scan is done approximately four hours after the injection. The DTPA “mimics” the flow of a radiolabeled antibody through the ommaya and also shows how well it is distributed through the intrathecal space. This test can be very frightening for some patients, since it is typically the first time the ommaya is accessed without the patient being on any pre-medications.
5. 8H9: Cycle One of Two (test and full doses). More information in Part 3 below.
  6. Brain/Spine MRI is done. Blood work is done 1-2+ times a week and weekly physical exams for approximately 2-3 weeks. As long as counts are within a specified range (liver values are monitored particularly closely) and the MRI is clear, the patient is given clearance to start the second cycle of 8H9.
  7. 8H9: Cycle Two of Two (test and full doses). More information in Part 3 below.
  8. Brain/Spine MRI to confirm patient can move to the next stage of the 8H9 protocol.
    - Blood work is done to determine if the patient is HAMA negative (i.e., has not developed a specific immune response to the 3F8 antibody during prior treatment) and if he/she is ready to start the 3F8 part of the protocol.
    - If the patient is HAMA negative: the necessary tests and scans are repeated and the patient is scheduled for 3F8 treatment.
    - If the patient is HAMA positive: the patient undergoes a specific drug regimen to try and become HAMA negative. This involves IV chemotherapy (Ritux/rituximab and Cytoxan/cyclophosphamide), oral chemotherapy (Temodar/temozolomide) and oral cisretinoic acid (Accutane). This treatment cycle is carefully planned by your medical team(s) and coordinated with you. HAMA blood work will be done at regular intervals to determine if the treatment is working. During this time, the regular battery of tests and scans are repeated every 3 months.
  9. 4 rounds of 3F8 with GM-CSF for systemic disease control (patient must be HAMA negative at the start of each cycle). If the patient becomes HAMA positive before a round of 3F8, the appropriate chemotherapy regime will be determined by the medical team so that the patient can ultimately become HAMA negative and continue the 3F8 therapy.

More information about the role of 3F8 in NB treatment can be found in Chapter 2, **—Understanding the Basics of Frontline Treatments—Overview of High Risk Treatment**; for information about the possible side effects of 3F8s and coping mechanisms some parents have found helpful, see Chapter 3, **—Coping with Treatment: Side Effects, Comfort, and Safety—Coping with 3F8 Antibodies.**

10. At the completion of the 3F8 therapy, the patient then does alternating cycles of oral temozolomide and Accutane for 6 months.

For information on administering Accutane and coping with its side effects, see Chapter 3, **—Coping with Treatment: Side Effects, Comfort Measures and Safety Precautions – Accutane.**

**Duration of Treatment:**

If the patient is able to complete the protocol without complications, delays and/or becoming HAMA positive, it is estimated that the entire treatment can take approximately 15 months to fully finish. However, complications and delays are not uncommon, and in the case of some patients the entire protocol can take upwards of two years or more. This can be a challenging situation for any family, and especially ones where long stays away from home are required. Many families find that the availability of the MSKCC Child Life and Social Work teams and the nearby Ronald MacDonal House facilities are valuable sources of support during the time in NYC.

**If MSKCC is not your Home Hospital:**

If you are an international patient or live a significant distance away from MSKCC, it may be possible to complete some parts of the treatment protocol in your home hospital. Whether or not this is possible must be determined in consultation with the MSKCC team, and if so, all details must be carefully coordinated with MSKCC and your local medical team. It may be possible to complete many scans, tests, and chemotherapy at your home hospital.

Also, keep in mind that if the patient is coming to MSKCC from another hospital, a long list of reports and samples must be pulled together for MSKCC (both in electronic and hard copy). It is crucial to begin work on this as soon as possible because collecting all of the reports, slides, and other information about the patient can take time. In general, it is very important to ensure that your home hospital and MSKCC are communicating well with one another so that details do not get missed and all aspects of the protocol are met properly.

For more information about traveling to New York City for treatment at MSKCC, see Chapter 13, **–Support Resources – Travel Guide: New York City/MSKCC.**

**Part 3: Administration of the 8H9 Antibody Treatments**

As noted above, in the MSKCC protocol as of 2012, two treatments of 8H9 are given, at least four weeks apart from each other. Each treatment consists of two doses, a test dose and the full therapeutic dose, typically given one week apart. If the therapeutic dose is delayed for any reason (e.g. low counts), it must be given within two weeks of the test dose or the test dose must be repeated. The 8H9 treatment is typically provided in the out-patient setting, with patients receiving the therapy in the Pediatric Day Hospital (PDH) at MSKCC. In the past, patients were admitted and the 8H9 treatment was done in-patient; however, this rarely happens now.

There are a number of required pre-medications which must be given before the test and therapeutic doses of 8H9:

**One Week Prior to the 8H9 Test Dose:**

Daily oral doses of SSKI (potassium iodide - for thyroid protection) and Cytomel (liothyronine - as a thyroid replacement therapy). These medications continue until two weeks past the last dose of 8H9. SSKI and Cytomel are well-tolerated medications.

**Prior to the 8H9 Test and Full Doses:**

Decadron (dexamethasone - for possible inflammation control) and Zantac (ranitidine - for possible allergic reaction) are given the day before, the day of, and the day after each dose of 8H9.

Clinic visits and blood work happen on the day before the 8H9 test dose to clear the patient for the formal start of treatment.

## **8H9 Test Dose**

### **On the Day of the 8H9 Test Dose:**

- The patient arrives at the hospital generally between 8am-9am and is given a room in the PDH (as noted, the treatment is only occasionally done as in-patient). A physical exam and blood work are done. After this, there may be a little bit of time to wait, giving a short opportunity to go to the playroom, use the computer, etc.
- Premedications begin around 10am. These generally include:
  - Zofran (ondansetron - 24 Hour Dose)
  - Vistaril (hydroxyzine) ○ Decadron (dexamethasone) ○ Zantac (ranitidine)
  - Tylenol (acetaminophen)
- The 8H9 typically arrives from Nuclear Medicine after lunch (somewhere between 1-2pm). The Nuclear Medicine team thoroughly checks to ensure that this dose is accurate and is being given to the correct patient. Given the presence of both the Oncology and Nuclear Medicine teams, there will be a lot of medical personnel in the room with you at this time.
- The ommaya reservoir is accessed and a sample of spinal fluid (~10ml) is removed from the patient. The 8H9 test dose is given through the ommaya reservoir and the patient remains accessed for the day. The line coming from the ommaya is carefully taped to the patient's head. Even though the patient is accessed, he/she is still able to move around, sit up in bed, watch TV, and even sleep if desired.
- Spinal fluid samples and blood work are taken approximately every hour for four hours after the 8H9 has been injected. A total of 4 CSF and 3 blood samples are taken.
- One hour after the 8H9 is given, a 24-hour dose of Ceftriaxone antibiotic is infused as a precautionary mechanism (against other possible sources of fever).
- Vistaril, Decadron and Zantac are given again at the end of the day.
- A CT/Pet scan is done. This takes approximately 30 minutes. The patient may be awake or sedated for the scan; however, he/she must be able to stay still for the entire time.
- Tylenol is taken every 4 hours for 24 hours after the 8H9 dose (and longer if a fever develops). Vistaril may also be given every 4-6 hours for 24 hours after the 8H9 dose.
- The day of the 8H9 test dose is a long day of activity. The patient may not be able to go home until well into the early evening.

### **For the Two Days after the 8H9 Test Dose:**

For two consecutive days after the test dose, the patient must go to clinic for the following:

1. Physical examination

2. Blood work
3. Ommaya tap with CSF sample taken
4. CT/Pet Scan (approximately 30 minutes)

## 8H9 Full Dose

One week after the 8H9 test dose, the full therapeutic 8H9 dose is given. Exactly the same procedures are followed as those outlined above for the test dose. However, generally there are NO scans required for this week (i.e., no CSF Flow Study or CT/Pet Scans).

After the full 8H9 dose is given, the Radiation Service team will go over all of the instructions on how to care for the patient. They will provide you with a letter outlining all of the instructions for patient care, and will have you sign a copy of this form for their records. As soon as the full dose of 8H9 is administered, the patient will be notably radioactive for a period of time and various precautions must be followed to ensure that people who are physically near the patient have limited radiation exposure. The following are some of the instructions that are provided:

For 24 Hours after the Full Dose:

- Keep the patient from public areas.
- Try to keep a distance of 3 feet from the patient.
- Keep the patient a distance of 6 feet from children and/or pregnant women.

For 2 Days after the Full Dose:

- The patient must sleep in a separate bed from other individuals (6 feet separation).

For 4 days after the Full Dose:

- The patient must not sleep in the same bed with children and/or pregnant women. □ Do not hold the patient in your arms for more than 30 minutes a day.

Some of the radioiodine will leave the patient's body through urine and bodily secretions. The following precautions must be taken because of this:

- After the patient has used the toilet, ensure that his/her hands are washed thoroughly with warm soapy water.
- Have the patient sit while urinating. Keep the toilet clean and if possible, wipe it down after it has been used by the patient.
- Wipe down the sink and bathtub after they have been used by the patient.
- Wash the patient's clothes, bed linens, and bathroom linens separately in warm water. If possible, also wash any plush toys.
- Handle any vomit or spit-ups with caution. If clean-up is required, be sure to wear gloves to protect your skin. If you are staying at the Ronald McDonald House, please discuss the proper disposal techniques for any vomit and diapers. If you have any concerns about safe clean-up, contact the Nuclear Medicine team or your medical team immediately.

Families considering future pregnancies should plan, if possible, to have Dad be the primary caregiver to the patient for 1-2 days after the full 8H9 dose. On the night of the full dose of 8H9, the patient and caregiver must stay at a hotel for the night, and not at the Ronald McDonald House. It is possible that this will be arranged for you by the MSKCC NB Social Worker; however, it is important to determine who is making the booking so that this does not get missed. If you are booking your own hotel room, the NB Social Worker will be able to give you a list of possible hotels that you can

stay at in the area. You may also be able to find a hotel at a good rate on your own through a personal points program or an online travel agency.

## Side Effects

Many families report that 8H9 is a fairly well-tolerated therapy, with patients experiencing few and manageable side effects.

Overall, patients may feel quite fatigued by the entire process due to all of the medications, the 8H9 itself, and the many procedures that are required. Each patient will respond differently to everything that occurs with the 8H9 protocol. Some may feel well for most of the procedures and be quite happy watching a movie, reading, and/or playing. However, other patients might prefer to sleep or relax quietly in their room. After the 8H9 test and full doses, patients may not feel up to their normal routines for that day and some of the days following the therapy.

The following are the most common side effects experienced by patients when receiving 8H9:

- Transient headache
- Nausea
- Fever
- Vomiting

The following are less likely side effects experienced by patients when receiving 8H9:

- Chemical meningitis (otherwise called a “chemical reaction” or “inflammation of the meninges”).
- A tingling sensation lasting a few minutes.
- Lowered counts requiring transfusions in the months following the treatment (this is mainly the case if cranio-spinal irradiation has been done prior to the 8H9 therapy).

It is important to address any side effects as they arise and to contact your medical team if you have any questions and/or concerns. Long-term side effects are rare, although some patients have required oral thyroid hormone replacement therapy.

## Part 4: Summary

It goes without saying that a diagnosis of a family member’s CNS relapse causes great anxiety and uncertainty. However, the good news is that there is a specific treatment available for this diagnosis, and one that many families have found to be well-tolerated by patients. The MSKCC medical team has been doing the 8H9 treatment since 2003, and will provide you with all the information you need to know, as well as the expert care needed by your family member. In addition, we hope that the information above from families who have been through the 8H9 protocol will be helpful to you when navigating this treatment. Finally, at MSKCC you are likely to meet other families whose children have been through the 8H9 treatment, some of them several years ago, and we hope these success stories will also help to sustain you.

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## Sources

Croog, V.J., Kramer, K., Cheung, N-K., Kushner, B.H., Modak, S., Souweidane, M.M., and Wolden, S.L. (2010) Whole Neuraxis Irradiation to Address Central Nervous System Relapse in High-Risk Neuroblastoma. *International Journal of Radiation Oncology Biol Phys.* Vol. 78, No. 3, 849-854.

Kramer, K., Kushner, B., Modak, S., Pandit-Taskar, N., Smith-Jones, P., Zanzonico, P., Humm, J.L., Xu, H., Wolden, S.L., Souweidane, M.M., Larson, S.M., and Cheung, N-K. (2010) Compartmental Intrathecal Radioimmunotherapy: Results for Treatment of Metastatic CNS Neuroblastoma. *Journal of Neurooncology*, 97, 409-418.

Kramer, K., Kushner, B., Heller, G., and Cheung, N.K., (2001) Neuroblastoma Metastatic to the Central Nervous System. The Memorial Sloan Kettering Cancer Center Experience and a Literature Review. *Cancer*, 91, 1510-1519.

Matthay, K.K., Brisse, H., Couanet, D., Couturier, J., Bernard, J., Mosseri, V., Edeline, V., Lumbroso, J., Valteau-Couanet, D., and Michon, J. (2003) Central Nervous System Metastases in Neuroblastoma: Radiologic, Clinical, and Biologic Features in 23 Patients. *Cancer*, 98, 155-165.

Modak, S., Guo, H.F., Humm, J.L., Smith-Jones, P.M., Larson, S.M., and Cheung, N-K. (2005) Radioimmunotargeting of Human Rhabdomyosarcoma Using Monoclonal Antibody 8H9. *Cancer Biother Radiopharm*, Oct 20 (5), 534-546.

Xu, H., Cheung, I.Y., Guo, H-F., and Cheung, N-K. (2009) MicroRNA miR-29 modulates expression of immunoinhibitory molecule B7-H3: Potential implications for immune based therapy of human solid tumors. *Cancer Res.* 2009 August 1; 69(15): 6275-6281. Also online at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719680/>

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