FEATURE ARTICLE

Evidence-Based Research for Intraperitoneal Chemotherapy in Epithelial Ovarian Cancer

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Intraperitoneal (IP) therapy is the administration of chemotherapy or biologic agents directly into the peritoneal cavity. A recent Gynecologic Oncology Group trial showed a survival advantage for women with advanced ovarian cancer and small residual disease after initial surgical staging and debulking who received IP therapy when compared to the standard IV regimen. The results prompted a National Cancer Institute announcement recommending the use of IP therapy in women who meet the criteria. This article describes the rationale for and underlying principles of IP therapy and summarizes the results of the three main clinical trials that led to the recommendation for incorporation of IP therapy into initial treatment of epithelial ovarian cancer.

In 2007, an estimated 22,430 women in the United States will be diagnosed with epithelial ovarian cancer and 15,280 will die of the disease (Jemal et al., 2007). Ovarian cancer is the leading cause of death in women with gynecologic malignancies. Since 1996 (McGuire et al.), the standard treatment for advanced-stage ovarian cancer has been surgical debulking, followed by six cycles of IV paclitaxel and carboplatin administered every 21 days. Despite the aggressive treatment and some improvement in five-year survival, the median survival for patients with the disease remains about 40 months. Because of the less-than-optimal results, treatments using novel drug combinations or high-intensity chemotherapy have been researched, but neither has produced evidence of clinical benefit or improved survival. Hence, when the results of a Gynecologic Oncology Group trial using intraperitoneal (IP) and IV chemotherapy agents known to be active in ovarian cancer confirmed a definite survival advantage in the IP arm when compared to the IV standard, the National Cancer Institute issued a clinical announcement that strongly suggested a change in standard practice for the initial chemotherapy regimen for the disease.

Although IP therapy is not a new method of drug delivery, it has been done principally as part of investigational research trials in cooperative groups' participating institutions or comprehensive cancer centers. Therefore, many clinicians and nurses outside of the research clinical trial setting are not familiar with IP therapy rationale and basic principles and guidelines for its administration in patients with ovarian cancer. This article will review the rationale, principles, and evidence-based research for the use of IP therapy in this population.

At a Glance

- Intraperitoneal (IP) therapy is the delivery of chemotherapy or biologic agents directly into the peritoneal cavity through a port and catheter.
- Results of a series of cooperative group clinical trials demonstrated improved survival for women who received IP therapy versus those who received only IV therapy.
- Basic principles of IP therapy must be adhered to for patient outcomes to be successful.

Use of Intraperitoneal Chemotherapy

Rationale

IP therapy is the delivery of chemotherapy or biologic agents directly into the peritoneal cavity. It has been studied in investigational research trials in tumors confined to the peritoneal cavity since the late 1970s. The therapeutic advantage is thought to be the ability to deliver a higher concentration of drug and a longer exposure of active drug that, over time, penetrates directly into small tumor tissue in the peritoneal cavity. In addition, the active

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chemotherapy, after first-pass metabolism in the liver, has a systemic cytotoxic effect through capillary flow into the tumor bed.

Dedrick, Myers, Bungay, and DeVita (1978) described the pharmacokinetic rationale of IP therapy using a mathematical model that suggests evidence about how chemicals move across the peritoneal membrane and are cleared from the systemic plasma. Dedrick et al.'s model demonstrated that, on average, the concentration of methotrexate or cytosine arabinoside (ara-C) in the peritoneal cavity was one to three logs greater than its concentration in the blood. Since that initial research, many other chemotherapeutic agents have demonstrated a peritoneal-plasma ratio that exceeds a 20-fold concentration difference. In particular, Howell et al. (1982) demonstrated that cisplatin peritoneal concentrations were 12–15 times greater than in the plasma; subsequently, Markman et al. (1992) reported a 1,000-fold difference in paclitaxel peritoneal-plasma concentrations. Many other chemotherapeutic and biologic agents also have been studied, and many show a similar pharmacokinetic advantage when administered through the IP route (Markman et al., 1989).

The peritoneal cavity can be thought of as a compartment that has dynamic properties of permeability and absorption of the body's naturally occurring electrolytes, chemicals, proteins, and fluids. Compartment, or local, drug therapy is not a new concept. It is the basic underlying rationale for intrathecal therapy that is used successfully in leukemia. Intrathecal therapy also takes advantage of the restricted transfer of drugs from cerebrospinal fluid (CSF) and has shown a twofold higher difference in CSF compared to plasma concentrations (Bleyer & Dedrick, 1977; Shapiro, Young, & Mehta, 1975). Applying the same rationale for the use of IP therapy also will exploit the peritoneal-plasma ratio to benefit tumor types such as ovarian cancer that remain principally confined to the peritoneum for their natural lives in the majority of women with cancer.

Principles

The basic principles of IP therapy are listed in Figure 1 and must be adhered to for successful outcomes to occur (e.g., response, increased survival).

Principle 1: The IP agent must have slow peritoneal clearance to maximize its direct exposure to the tumor. In contrast, when the agent reaches the systemic circulation, rapid clearance is necessary to minimize the toxicity of high-dose therapy (Dedrick, 1985; Dedrick et al., 1978; Markman et al., 1989; Markman & Walker, 2006). In the peritoneal cavity and the systemic circulation, the agent must maintain its anticancer properties.

1. The agent should have slow peritoneal clearance and rapid systemic clearance and should demonstrate activity against the tumor type.
2. The agent should have rapid and extensive hepatic metabolism into nontoxic metabolites during first pass through the liver.
3. Intraperitoneal tumors should be small, preferably less than 0.5 cm in greatest dimension.
4. Large treatment volumes are needed to ensure direct exposure of the agent to all peritoneal surfaces.
5. Administration of intraperitoneal therapy should be done through a port connected to a catheter that floats freely in the peritoneal cavity.

Figure 1. Principles of Intraperitoneal Therapy

Note. Based on information from Dedrick et al., 1978; Markman et al., 1989.

Principle 2: The agent administered preferably is metabolized during the first pass through the liver into nontoxic metabolites. Most metabolism of peritoneal agents enters systemic circulation through the portal circulation (Kraft, Tompkins, & Jesseh, 1968). To minimize systemic toxicity, nontoxic metabolites need to enter the circulation. Similarly, drugs that compete for hepatic or renal clearance with the anticancer agents should not be coadministered to lessen the potential for more severe systemic toxicity (Dedrick et al., 1978). Women with severely compromised renal or hepatic function may have more severe toxicity, and adequate preventive measures need to be employed prior to IP therapy.

Principle 3: The individual tumor size must be small (Alberts et al., 1996; Dedrick et al., 1978; Howell et al., 1982). The IP agent is limited and dependent on direct tumor diffusion in the peritoneal cavity and blood perfusion through capillary flow once the agent enters the systemic circulation. If the tumor size is larger than a few millimeters in greatest dimension, the diffusibilty of the agent is limited and a less-than-desirable response can be anticipated. A recent debulking laparotomy, preferably performed by a gynecologic oncologist, leaving either no gross residual or visible tumor greater than 0.5 cm in dimension prior to IP therapy, offers the best opportunity for an optimal response. However, the current IP standard is based on the Armstrong et al. (2006) trial, where eligibility was no tumor greater than 1 cm in dimension prior to IP.

Principle 4: Sufficient volume of distillate with the antitumor agent must be instilled to ensure exposure of the agent and optimize the drug distribution to the entire peritoneal cavity (Alberts et al., 1996; Armstrong et al., 2006; Dedrick et al., 1978; Markman et al., 1989, 1992, 2001). All clinical trials that have demonstrated better response with IP versus IV therapy have used a volume of 2 L of normal saline solution in the peritoneal cavity. Although the principle is probably responsible for most of the toxicities related to IP therapy (i.e., abdominal bloating, pain, and temporary shortness of breath), it is important and cannot be modified without the possibility of compromising maximum tumor response.

Principle 5: IP therapy should be administered through a port connected to a catheter that floats freely in the peritoneal cavity. The access system has evolved over time from a single-use percutaneous catheter placed and removed at each treatment to a transcutaneous, semipermanent catheter system and, finally, to the current subcutaneously placed, semipermanent port and catheter system. More research is needed to determine which type of catheter provides the best delivery and fewest catheter-related problems. Currently, studies recommend either a single-lumen polyurethane IV catheter or a fenestrated semipermanent catheter. Additional research may determine whether one of the catheters is superior. Complications related to the catheter and access system will be discussed in the article on pp. 221–225.

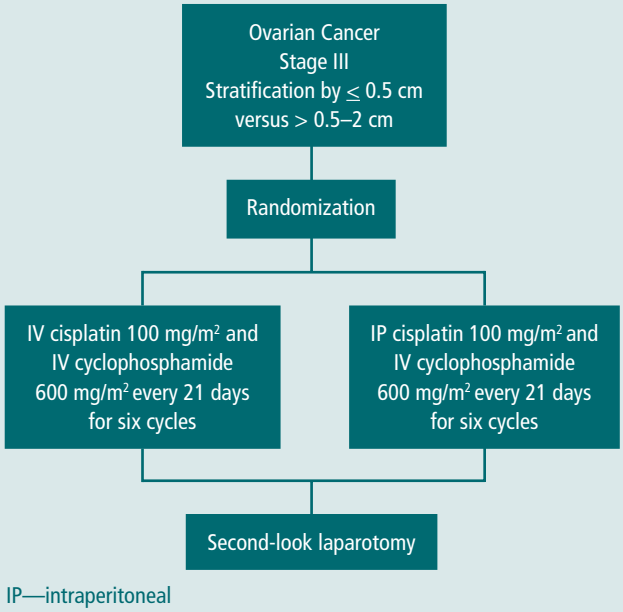
Evidence-Based Research

Data from phase I and II trials in the literature during the 1980s and early 1990s describe the potential response benefit of IP therapy when administered to women who meet the criteria for optimum response (e.g., small-volume disease confined to the peritoneal cavity with the potential for good peritoneal distribution of the anticancer agent) and have not demonstrated resistance to the particular chemotherapeutic agent. However, cooperative groups enlisted patients in phase III clinical trials that studied

other experimental IV regimens that incorporated either high-dose chemotherapy or multiple sequential agents using the known standard active agents. Results of intergroup trials (Southwest Oncology Group, Eastern Cooperative Oncology Group, and Gynecologic Oncology Group) by Alberts et al. in 1996 and Markman et al. in 2001, however, generated provocative results that initiated a third trial in the Gynecologic Oncology Group alone, recently published by Armstrong et al. (2006). Following are brief summaries of each of the major phase III IP trials.

IV Cisplatin and Cyclophosphamide Versus IP Cisplatin and IV Cyclophosphamide

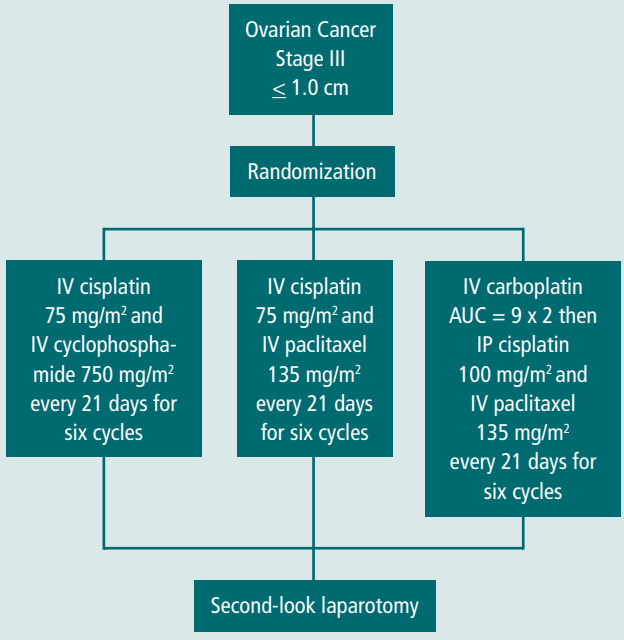
Conducted from June 1986–July 1992, this trial enrolled 654 women (546 eligible for evaluation) with pathologically confirmed stage III epithelial ovarian cancer who, after surgical debulking, had no tumor nodules greater than 2 cm in dimension (see Figure 2). Each woman was stratified by size of the largest tumor after debulking surgery (< 0.5 cm versus > 0.5–2 cm) and then randomized to receive either standard IV cisplatin and cyclophosphamide or the investigational arm of IP cisplatin and IV cyclophosphamide. Each regimen was given at three-week intervals for six cycles. Results confirmed a modest survival advantage in the IP group (41 versus 47 months, respectively; $p = 0.02$). Covariates that determined survival included absence of gross disease at enrollment ($p < 0.001$), younger age ($p < 0.001$), tumor type other than clear cell or mucinous carcinoma ($p < 0.001$), and enrollment after surgery ($p < 0.001$) (Alberts et al., 1996). Conclusions of this trial demonstrated that a modest overall survival advantage was achieved in the IP group. However, another Gynecologic Oncology Group trial done during the same time period as the IP trial compared standard IV cisplatin and cyclophosphamide versus IV paclitaxel and cisplatin. Results of that trial suggested a significant survival time in the IV paclitaxel and cisplatin arm (McGuire et al., 1996).



IP—intraperitoneal

Figure 2. Gynecologic Oncology Group Trial 104 and Southwestern Oncology Group Trial 8501

Note. Based on information from Alberts et al., 1996.



AUC—area under the curve; IP—intraperitoneal

Figure 3. Gynecologic Oncology Group Trial 114

Note. Based on information from Markman et al., 2001.

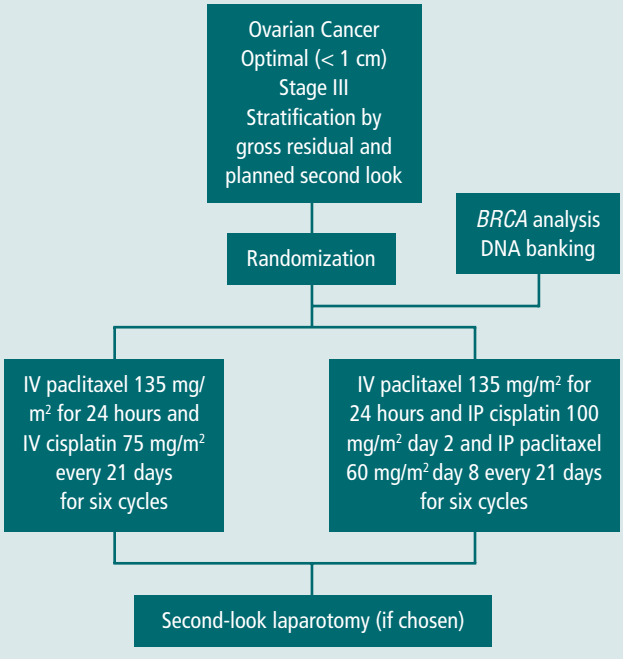
Therefore, the IV regimen became the new gold standard, and the researchers advised that IP therapy needed further study.

IV Paclitaxel and Cisplatin Versus Moderately High-Dose Carboplatin and IV Paclitaxel and IP Cisplatin

Conducted from August 1992–April 1995, this trial enrolled 523 women (462 eligible for evaluation) with pathologically confirmed stage III epithelial ovarian cancer and largest residual tumor ≤ 1 cm in diameter after surgical debulking (see Figure 3). The original trial had three arms. One arm included standard cisplatin and cyclophosphamide, but after the results of the paclitaxel and cisplatin trial became known, the arm was discontinued. The other two arms included the new standard IV paclitaxel and cisplatin versus IV carboplatin for two cycles followed by IP cisplatin and IV paclitaxel for six cycles. Results showed modest improvement in progression-free ($p = 0.01$, one-tailed) and overall ($p = 0.05$, one-tailed) survival in the experimental group, but the improvement likely was explained by the two extra cycles given to women in the experimental arm of the trial rather than the IP route administration (Markman et al., 2001). However, further exploration with IP therapy was initiated by the Gynecologic Oncology Group.

24-Hour IV Paclitaxel and Cisplatin on Day 2 Versus 24-Hour IV Paclitaxel and IP Cisplatin on Day 2 and IP Paclitaxel on Day 8

Conducted from March 1998–January 2001, this Gynecologic Oncology Group trial enrolled 429 women (415 eligible for evaluation) with pathologically confirmed epithelial ovarian or primary peritoneal cancer with no residual disease mass greater than 1 cm after surgical debulking (see Figure 4). The trial randomized one group to the standard IV paclitaxel and cisplatin



IP—intraperitoneal

Figure 4. Gynecologic Oncology Group Trial 172

Note. Based on information from Armstrong et al., 2006.

and a second group to IV paclitaxel and IP cisplatin and then IP paclitaxel on day eight of the 21-day regimen for each arm for six cycles. Results showed that the experimental arm had a progression-free survival advantage of 18.3 versus 23.8 months ($p = 0.05$ by the log-rank test) and an overall survival advantage of 49.5 months versus 66.9 months ($p = 0.03$ by the log-rank test). The trial reported the longest survival in women with advanced ovarian cancer, and the advantage was in women in the IP arm of the trial (Armstrong et al., 2006).

Although the trial's results support further use of IP therapy in advanced ovarian cancer, the toxicity profile for this mode of therapy was higher than in the standard arm, and quality-of-life during treatment also was reduced. IP catheter complications were the major reason for discontinuation of therapy.

Conclusion

With the introduction of any new treatment regimen or mode of administration such as IP therapy, a learning curve is expected for all health professionals involved in the care of patients receiving such therapy. Understanding the rationale and principles that underlie the basic premises of IP therapy is the first step needed in the educational process to ensure successful treatment and avoid, or at least lessen, the complications that are associated with IP therapy. As nurses become more familiar with how to access the IP port and the correct way to administer therapy directly into the peritoneal cavity, the same or better survival benefit may be observed without increasing toxicity or having to sacrifice quality of life during treatment. The articles on pp. 201–207 and pp. 221–225 review the recommended nursing performance competency checklist for IP therapy and related patient education. See Appendix for a patient guide to IP therapy.

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Appendix. Your Guide to Intraperitoneal Therapy

Lois Almadrones, RN, MPA, FNP, Anne Marie Flaherty, RN, MS, and Catherine Hydzik, RN, MS, AOCN®

Introduction

This booklet is designed to provide you with information about intraperitoneal therapy and prepare you to participate in activities which will assist you during the time you receive this therapy.

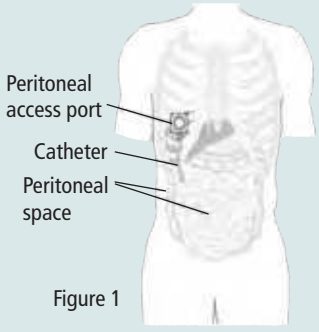

Figure 1

What Intraperitoneal Therapy Is

Intraperitoneal therapy is the delivery of anti-cancer drugs directly into the peritoneal space (abdominal cavity). This space lies between the abdominal muscles and abdominal organs. The anti-cancer drug is mixed in a large volume of fluid and instilled into the peritoneal space through a port and catheter. Your surgeon will insert a peritoneal access port into a pocket beneath the skin near your rib cage. (See Figure 1.)

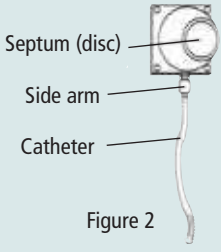

Figure 2

The port consists of a raised chamber. Imbedded into the top of the chamber is a self-sealing silicone rubber septum (disc). The chamber also has a side arm for attaching the flexible catheter, which is placed in your peritoneal space. (See Figure 2.) Your surgeon usually inserts the port and catheter at the time of your surgery.

Intraperitoneal therapy allows direct contact of the cancer-fighting drug with the cancer within your peritoneal space. The drug is left in the peritoneal space to "bathe" the cancer. This method of delivering it directly into the cavity where the cancer is located allows a higher concentration of the drug to be given.

Where Your Intraperitoneal Therapy Will Be Administered

Intraperitoneal therapy may be given in the inpatient or outpatient setting. Where you receive your intraperitoneal therapy, how many treatments you receive, and the duration of therapy depend on your condition and the particular anti-cancer drug your doctor has recommended.

During the actual treatment you will be asked to remain in your bed.

Who Will Administer Your Intraperitoneal Therapy

Your intraperitoneal therapy will be administered by a registered nurse. Your nurse will review with you information explained in this booklet as well as review the Chemotherapy Fact Card about your anti-cancer drug. The Chemotherapy Fact Cards contain the important information you need to know about the drugs you will receive.

How Your Intraperitoneal Therapy Will Be Administered

Before and during the intraperitoneal treatment, intravenous fluid may be administered through a vein. The purpose of this fluid is to maintain your fluid level and to allow the administration of antinausea medicine if it is necessary during your treatment.

To begin your intraperitoneal therapy, the nurse will place a special needle though your skin and into the self-sealing septum in the port chamber. This will feel similar to a small pin prick. The needle will be taped securely and covered with a small dressing. A fluid administration set, which contains the anti-cancer drug, will be attached to the needle. The volume of fluid your medication is mixed in is determined by the treatment you are receiving. This amount is given to allow the drug to reach and "bathe" all parts of the peritoneal space. The solution will be allowed to flow into your peritoneal space by gravity. The actual intraperitoneal therapy treatment time varies, but it is usually no more than 1 1/2 to 2 hours. More solution may be ordered after the treatment to improve the bathing of the peritoneal space.

After the solution has flowed into your intraperitoneal space, the special needle will be removed and a bandage will be placed on the site. This bandage can be removed after about 30 minutes. Your nurse will ask you to move from side to side in bed a few times. This will help to distribute the anti-cancer drug solution evenly throughout your peritoneal space. Your intraperitoneal therapy will then be complete and you may be out of bed as desired. The solution in your peritoneal space will be absorbed by your body over the next few days. During this time, your abdomen may be bloated and you may feel some abdominal pressure.

What to Do at Home to Prepare for Your Intraperitoneal Treatment

- Wear expandable or loose-fitting clothing to the hospital.
- Eat a light dinner the night before and a light breakfast the morning of the treatment.
- If you wish, bring a cassette or CD player or iPod® and your favorite music to listen to during treatment. A television is provided in the room where you receive your treatment.
- It may be helpful to have a relative or friend accompany you home as some medicine may make you feel drowsy.

Possible Side Effects of Intraperitoneal Therapy and Comfort Measures to Minimize These Effects

You may not experience any side effects from your intraperitoneal therapy. The following are some effects that some patients have reported, and the comfort measures they have found helpful.

POSSIBLE SIDE EFFECTS	COMFORT MEASURES
Abdominal pressure and bloating (caused by the large volume of fluid injected into the peritoneal space)	Walk around after the treatment is completed. Wear comfortable clothing with an expandable waistline, especially for the first few days after treatment.
Frequent urination/ bladder fullness (a desired side effect caused by the intravenous fluids)	Empty your bladder just before beginning treatment. You will be allowed to use the bathroom, if needed, during the treatment.
Breathing faster and more frequently (caused by the large volume of fluid injected into the peritoneal space)	Elevate the head of your bed during treatment. Walk around after the treatment. Sit in an upright chair after the treatment.
Nausea, vomiting, or both (caused by anti-cancer drugs)	Antinausea medicine may be given to you before, during the therapy, or both. Your doctor will prescribe antinausea medicine for you to take at home if needed.
Decrease in appetite (caused by large volume of fluid injected into the peritoneal space and anti-cancer drugs)	Eat smaller meals more frequently. Drink high nutrition liquid supplements.

Some of the drug you receive is absorbed and carried throughout your body. The effects you feel may be caused by the drug(s) given to you.

What You Need to Know About Home Care of the Peritoneal Port

- Since the peritoneal access port is located under your skin, no covering or bandage is required.
- You may bathe or shower.
- Having a port and catheter in place should not restrict your activities. Reasonable exercise is allowed after the incision is healed and your recovery from other surgery is complete. Ask your doctor or nurse about resuming your normal activities.
- Inspect the skin around your port daily. If this area becomes reddened, swollen, or tender to the touch, you should report this to your doctor or nurse.
- The port and catheter do not affect your dietary habits. You may continue on the diet which you normally eat.

When You Should Notify Your Doctor

Call your doctor if you:

- Experience unusual abdominal pain.
- Have a fever of 101° F (38.3° C) or higher.
- Develop redness, swelling, or tenderness around the port site.
- Have severe nausea, vomiting, diarrhea, or constipation that lasts more than 24 hours.
- Are unable to eat or drink for more than 24 hours.
- Have any unexpected or unexplained problems.

Questions for Your Doctor or Nurse

The following section is where you may write any questions or comments you have about intraperitoneal therapy. We encourage you to discuss your therapy and any additional questions you have with your doctor or nurse.

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