Royal: The Fifth Shade of Blue

RICHARD LAM, M.D.
MARK SCHOLZ, M.D.
PATRICIA CHANG, M.D.

Prostate cancer comes in many forms and presents at different stages.

To simplify, we divide it into categories, or "shades" of Blue. The first three shades - Sky, Teal and Azure - represent the commonly described Low, Intermediate and High-Risk categories of men who have never had surgery or radiation (local therapy). The fourth and fifth Shades, Indigo and Royal, represent men who have Relapsed and Advanced disease, respectively (see table).

Men in the Royal category have either confirmed spread of cancer to a distant area of the body other than the pelvic lymph nodes, a PSA above 100 or a rising PSA despite negligible testosterone levels in the blood.

	Local Therapy	Gleason Score	% Cores with cancer	PSA Level	Rectal Exam	Endorectal MRI & CT	Bone Scan
Sky(1)	No	<7	<34%(2)	<10	No Nodule	No ECE	No Need
Teal(3)	No	7	34-50%	10-20	Small Nodule	No ECE	Clear
Azure	No	>7	>50%	>20	Large Nodule	ECE/SV/PN	Clear
Indigo	Yes	Any	Any	<100	Any	Pelvic Node	Clear
Royal	Yes/No	Any	Any	>100	Any	Other Node	Positive

1. To qualify into Sky, all the results must meet the criteria of the top row.
2. A single core having more than 50% cancer bumps the category to Teal.
3. Two or more factors in the Teal row bumps the category to Azure.

ECE = Extra-capsular Extension, SV = Seminal Vesicle, PN = Pelvic node

Treatment for men in the Royal category has become much more complex in the last couple of years, and for a good reason: So many new treatment options are available to patients in this group.

In the old days, men in the Royal blue category with less advanced or slower-growing prostate cancer were treated with ketoconazole or estrogen. Men with more aggressive disease received Taxotere, Mitoxantrone or spot radiation.

Now Provenge®, Zytiga® (abiraterone) and Jevtana (cabazitaxel) are on the market. MDV-3100 (enzalutamide) and Alpharadin® will likely be FDA-approved soon. Additionally, an abundance of exciting new investigational agents such as Prostavac®, Ipilimumab (Yervoy®), Custirsen (OGX-011), TAK-700, XL-184 and Tasquinimod, medicines that make a significant difference, are available via clinical trials. There are many unanswered questions about selecting the proper sequence.

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Let's start with the four basic principles of treatment for men in Royal:

1. **Start early and begin with the best therapy.** The "best therapy" is the one that is most likely to be effective without incurring excessive side effects. At Prostate Oncology Specialists, we consider "holding the best treatment in reserve" to be a losing strategy, because it allows the cancer to become more entrenched and will result in lower response rates.

Sequencing treatment has become an even more weighty issue, because access to new investigational agents is determined by each patient's exposure to previous treatment. Selecting one treatment may close the door on another.

2. **Monitor the situation closely.** Prostate cancer is a dynamically changing situation, and special attention needs to be given to determine when a treatment is no longer working. Precious time can be lost by staying on an ineffective treatment when many good alternatives have yet to be tried.

In general, after starting most new treatments, it usually takes 60-90 days to determine whether it is working. A reduction in pain (if present) is usually the first sign that a treatment is effective. This is usually followed by a decline in blood markers such as PSA, PAP, LDH, ALP and CTC (circulating tumor cells). Bone scans and CT scans show changes more slowly. (Improvement in PET scans occur faster, usually within 30-60 days).

3. **Treatment selection is influenced by disease severity.** Disease severity is judged by its extent (few or many spots on a bone scan) and rate of progression (cancer symptoms of pain or PSA rapidly rising). With extensive or rapidly progressing disease, it may be necessary to forgo hormonal and immune treatments and jump directly to chemotherapy.

4. **Physical Strength and Bones.** Physical strength is sapped by advancing age, low testosterone levels and chemotherapy. This is why resistance training with weights under the supervision of a trainer is essential.

Prostate cancer and low testosterone levels can also weaken the bones. Unless there are medical contraindications, everyone in the Royal category should be taking Xgeva or Zometa. Spot radiation to the bones, long considered standard in the management of bone metastases, should be used sparingly. Excessive bone radiation cripples the immune system and limits future treatment options.

Most men in Royal have already been taking hormone therapy, such as Lupron®, Trelstar® or Zoladex®. The majority of this article is about what to do when the disease progresses after already being on Lupron for some time. However, some men in Royal have high PSA levels and positive bone scans at the time of diagnosis.

Obviously, men in the Royal shade who have never had hormone therapy should probably start. We have active Royal-category patients in our practice who have taken Lupron alone, with PSA levels maintained at less than 0.1 for more than ten years. Unfortunately, such favorable long-term results only occur in a minority of patients. Therefore, we routinely use upfront Casodex and Avodart (or Proscar). If there are only a couple of bone metastases, we consider adding spot radiation.

If the PSA fails to drop below 0.1 with Lupron, Casodex and Avodart (known as a high PSA nadir), this usually indicates that the PSA will soon rise. The next step is to stop the Casodex. Rarely, the PSA will go down for a short period of time after stopping Casodex. ***(continued on page 7)***

When PSA starts to rise, if the pace of disease progression is slow, then our next step is to start Provenge, followed by Zytiga (Provenge is only covered by insurance when the PSA is rising. If Zytiga is started first, the PSA will drop and Provenge will have to be postponed until the Zytiga stops working).

If insurance coverage is confirmed, Zytiga can usually be started right after Provenge. Zytiga is normally given with prednisone. However, since prednisone can diminish the immune effects of Provenge, we recommend substituting another medication called Inspra for the prednisone.

Clinical Trial Alternative #1

Prostavac is a new immune treatment only available in a clinical trial. Men who have had Provenge are excluded from this trial. Rather than starting Provenge immediately, some men may prefer to participate in the Prostavac trial, and plan to use Provenge afterward. The results of a preliminary study demonstrated a substantial prolongation of survival in men treated with Prostavac.

Zytiga is very effective and quite well-tolerated. Three months after treatment with Provenge, we recommend stopping Inspra and starting prednisone. Prednisone enhances Zytiga's effectiveness.

The next step in our clinic, if the cancer starts to progress while taking Zytiga, is Taxotere. Taxotere is most effective when given every three weeks in a larger dose. However, it is much better tolerated when given weekly in smaller doses. Due to its rapid onset of action, Taxotere is considered the first step for men whose cancer is progressing rapidly or causing pain.

Taxotere's effectiveness can be further enhanced by combining it with other chemotherapies, such as Carboplatin, Xeloda or Emcyt. The most active protocol that has been reported to date is a combination of Taxotere, Avastin and Revlimid. Practically everyone will experience a dramatic decline in PSA with these three drugs. However, as expected, side effects, including osteonecrosis of the jaw, occur much more frequently.

Clinical Trial Alternative #2

Tasquinimod is a potent new anti-angiogenesis (strangulates the cancer by cutting off its blood supply) medication. The attractive aspect of this drug is that it can be taken orally.

Clinical Trial Alternative #3

A new medicine called **Custirsen** that substantially enhances Taxotere's effectiveness is being studied in a clinical trial. Half the men get Taxotere and the other half receive the combination of Custirsen plus Taxotere. Side effects from adding Custirsen to the Taxotere are mild. A preliminary report of Taxotere and Custirsen showed a 60% increase in survival compared to Taxotere alone.

A number of additional types of chemotherapy, including Mitoxantrone, Adriamycin, Velban and Flurouracil, can be considered if resistance to Taxotere develops. However, a large randomized trial in 2009 clearly showed that Cabazitaxel (Jevatana) is effective in men who have become resistant to Taxotere. Therefore, Cabazitaxel should be the first consideration in men who are Taxotere-resistant.

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Clinical Trial Alternative #4

XL-184 is a new medication being studied in two different Phase III trials in men who are resistant to Zytiga and Taxotere. The first trial will evaluate the effectiveness of XL-184 compared to Mitoxantrone for controlling pain. The second trial will evaluate the effect of XL-184 on survival. Preliminary studies of XL-184 have shown rapid resolution of pain and rapid disappearance of cancer abnormalities seen in bone scans.

Clinical Trial Alternative #5

MDV-3100 is a new, very active agent that will likely be available by the summer of 2012 in an expanded access trial. Medivation, the company that owns MDV-3100, anticipates FDA approval by the end of the year. In the meantime, they plan to distribute MDV-3100 free of charge to men with progressive prostate cancer who have progressed on Taxotere.

Clinical Trial Alternative #6

Alpharadin is a new bone-targeted agent that has been shown to alleviate bone pain and prevent skeletal fractures. More importantly, its bone-protecting effects are so profound that it has been shown to prolong life. This agent is expected to be FDA-approved in 2012, and is also available through an expanded access trial (see page 26).

Clinical Trial Alternative #7

TAK-700 (Ortoronel) is a new hormone agent similar to abiraterone (Zytiga). Studies are currently being conducted in two types of patients with metastatic disease: Those who have not received Taxotere and those who progressed despite Taxotere.

The therapeutic landscape for advanced prostate cancer is rapidly charging ahead. We now have four FDA-approved interventions that have been shown to prolong the lives of patients with advanced metastatic disease.

The selection of the best treatment plan is only possible after carefully reviewing all available options and creating a tailored plan specifically for each individual. This means assessing the patient's cancer volume and growth velocity, as well as his ability to tolerate treatment.

As more options become FDA-approved in the near future, clinicians will be able to manage a disease, once thought to be rapidly fatal, as a chronic condition. Survival will be measured in years, not months. Furthermore, clinicians will have the opportunity to see even better results by using these medications together in exciting new combinations. ◆

Visit the Prostate Cancer Blue Community at www.pcribc.org to learn more about SHADES, network with other men in your category and talk to PCRI Helpline mentors!