

COUNTERPOINTS

Current Controversies in Hematology and Oncology

Is There a Clinical Role for Molecular Phenotyping in Atypical Presentation of Metastatic Castration-Resistant Prostate Cancer?

Now that our understanding of potentially actionable mutations has increased, is it time for physicians to look into molecular phenotyping for their patients with metastatic castration-resistant prostate cancer? Or should physicians be looking elsewhere for guidance on treating this heterogeneous disease? Here, Drs David J. VanderWeele and Walter M. Stadler make the case for molecular phenotyping in these patients, whereas Dr Nicholas J. Vogelzang argues that alternative approaches hold more promise.

The Time for Molecular Phenotyping of Metastatic Castrate-Resistant Prostate Cancer is Now



David J. VanderWeele, MD, is an instructor of medicine at the University of Chicago Medicine in Chicago, Illinois.



Walter M. Stadler, MD, is the Fred C. Buffett Professor of Medicine and Surgery, chief of the section of hematology/oncology, and director of the genitourinary program at the University of Chicago Medicine in Chicago, Illinois.

The treatment of advanced prostate cancer has benefitted from the early use of targeted therapy; that is, androgen ablation via surgical or chemical castration.¹ The initial dependence of the vast majority of prostate cancers on the androgen receptor (AR), and a paucity of alternative treatment options, traditionally have made further molecular testing for advanced prostate cancer largely irrelevant. The number of genetic tests incorporated into common clinical practice is zero.

Now, however, there is increased acknowledgement of prostate cancer heterogeneity, and an increasing number of treatment options are available. We also are beginning to identify potentially targetable alterations. The most comprehensive study performed to date has estimated that more than 89% of patients with metastatic castration-resistant prostate cancer (mCRPC) have a potentially targetable alteration.² With the incorporation

(continued on page 581)

There Is No Current Role for Molecular Phenotyping in Metastatic Castrate-Resistant Prostate Cancer



Nicholas J. Vogelzang, MD, is a member of the Research Executive Committee and Chair of the Genitourinary Committee at US Oncology Research. He is a full-time genitourinary oncologist with Comprehensive Cancer Centers of Nevada and a clinical professor of medicine at the University of Nevada School of Medicine in Las Vegas and Reno, Nevada.

Unfortunately, there is no current role for molecular phenotyping in metastatic CRPC.

A major impediment to molecular phenotyping is the fact that prostate cancer shows tremendous heterogeneity in its end stages. This heterogeneity has been well demonstrated by several rapid (“warm”) autopsy series.^{1,2,3} The study by Grasso and colleagues identified low overall mutation rates even in heavily treated CRPC, and was not able to identify any mutation with an incidence of greater than 8%.

These data were confirmed in 2 studies presented at the most recent American Society of Clinical Oncology (ASCO) annual meeting, by Small and colleagues⁴ and by Beltran and colleagues.⁵ Both of these studies showed a significant degree of histologic and molecular heterogeneity in these advanced prostate cancer patients. A dominant driver mutation or amplification for metastatic CRPC has not been identified. A working hypothesis is that AR-driven prostate cancer evolves into a heterogeneous horde of

(continued on page 584)

(continued from page 580)

The Time for Molecular Phenotyping of Metastatic Castrate-Resistant Prostate Cancer is Now (cont)

of molecular phenotyping into clinical practice, coupled with emerging resources to track responses, we can rapidly advance the management of advanced prostate cancer.

Recent Advances in Therapies and Testing

Recent advances have led to the approval of 5 new therapies over the past 5 years that improve overall survival (OS), including 2 agents that more potently inhibit androgen signaling: abiraterone acetate (Zytiga, Janssen Biotech) and enzalutamide (Xtandi, Astellas/Medivation). Though these agents have improved outcomes for those with mCRPC, multiple mechanisms of resistance to abiraterone and enzalutamide can confer primary or secondary resistance. These include AR-specific mechanisms, such as expression of AR splice variants, specific mutations in the AR gene, and overexpression of AR³⁻⁷; activation of alternative nuclear factors^{8,9}; and activation of alternative pathways.¹⁰

Molecular tests may soon help guide decisions regarding AR pathway therapies. Though these results need to be validated, expression of the AR splice variant V7 (AR-V7) in circulating tumor cells (CTCs) predicts a very low response rate to abiraterone or enzalutamide.¹¹ Despite evidence that docetaxel works by keeping AR out of the nucleus,¹² AR-V7 expression appears to be a treatment-selection marker for taxanes.¹³ Other CTC-based biomarkers, including morphologic and biologic features such as nuclear speckling and loss of AR C-terminal staining, are being validated for predicting better outcomes with taxanes than with AR-targeted therapies.¹⁴

Histologic Variations

AR alterations not only predict resistance to AR pathway therapies, but also appear to define a new phenotype. The Stand Up to Cancer's West Coast "Dream Team" has found that more than one-quarter of cancers resistant to abiraterone and enzalutamide have a histologic phenotype distinct from pure adenocarcinoma and small cell cancer, which they term intermediate atypical carcinoma (IAC). Another third of patients have mixed histologies.¹⁵ Gene expression assays identified a decrease in AR activity in small cell cancer, along with alterations in many other pathways, and IAC was shown to be intermediate between adenocarcinoma and small cell cancer. Outcomes with standard therapies are worse for IAC—similar to pure small cell histologies—though suitable alternative therapy options have not been identified yet.

Beltran and colleagues performed a comparison between conventional CRPC and what they termed neuroendocrine prostate cancer (NEPC), which is characterized by low or absent AR expression and extensive neuroendocrine differentiation (small, round, blue neuroendocrine cells that express neuroendocrine markers). They found a similar rate of nonsynonymous mutations and a similar percentage of the genome involved with copy number changes between these 2 histologies.¹⁶ As seen with IAC, there is decreased AR signaling in NEPC, and AR mutations were absent in CRPC. Moreover, NEPC is enriched for alterations in *AURKA*, *MYCN*, *RB1*, *TP53*, and *CDKN1B*.^{16,17} This has led to clinical trials testing the efficacy of the Aurora kinase A (AURKA) inhibitor MLN8237 in NEPC (NCT01094288, NCT01799278). Interestingly, the authors found evidence of divergent clonal evolution rather than linear progression, suggesting

More than 89% of patients have a potentially targetable alteration.

coexistence of NEPC and CRPC within a given patient and supporting the need for increased use of biopsies to characterize progressing metastases.

Biomarker-Driven Therapies

In addition to identifying an intermediate or NEPC-like phenotype, there is mounting evidence that genomic alterations in conventional CRPC are associated with susceptibility to specific targeted therapies. It has long been recognized that *PTEN* deletion is a common event in advanced disease and also can be found in localized disease, often at the subclonal level, with up to 100% of advanced disease harboring alterations in the PTEN/phosphoinositide 3-kinase (PI3K)/AKT pathway.¹⁸⁻²¹ Newer data have demonstrated alterations in the *PIK3CA* and *PIK3CB* genes. Inhibitors of the PI3K pathway have yielded disappointing results, but recent preclinical data suggest that inhibition of both *PIK3CA* and *PIK3CB* in the setting of AR antagonism can result in exceptional responses.^{10,22}

Patients with germline *BRCA2* alterations are more likely to develop prostate cancer, and the disease is more

likely to be aggressive.^{23,24} As in other tumors, *BRCA1* or *BRCA2* alterations predict response to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in prostate cancer, some of them prolonged.²⁵⁻²⁷ Alterations in the ataxia-telangiectasia mutated (ATM) protein kinase have been associated with objective response to PARP inhibitors,²⁸ as have biallelic loss of Fanconi anemia complementation group genes and *CHEK2*.²⁹ As the list of genes associated with response is better defined, the number of potential responders to PARP inhibitor-based therapy will continue to grow.

Since the identification of erythroblast transformation-specific (ETS) transcription family translocations in approximately half of all prostate cancers,³⁰ the clinical implication of these translocations has been debated. There are now preclinical data supporting the role of PARP inhibitors for patients with ETS family translocations,³¹ and clinical trials are underway to test their efficacy in the clinical setting (NCT01972217). Indeed, many with objective responses to PARP inhibitors have alterations in both *BRCA2* and the ETS family member *ERG*.²⁶

Use of platinum agents is typically reserved for those with the small cell phenotype or neuroendocrine disease. It was recently reported that a patient with liver and lung metastases had a complete response to carboplatin-based therapy, and in vitro data suggest that the sensitivity to platinum was conferred by a *FANCA* alteration.³² Approximately 36% of patients with end-stage disease have an alteration in at least 1 Fanconi anemia gene.¹⁸

Rare fusions have been identified in *RAF* genes³³ and Wnt signaling pathway family members.² These suggest that the use of RAF or MEK inhibitors or porcupine inhibitors,³⁴ respectively, might be effective. *RBI* loss and alterations in other cell-cycle genes is common (~25% of cases), both in NEPC and conventional CRPC. New cyclin-dependent kinase (CDK) inhibitors may be effective in patients harboring these alterations,³⁵ and a phase 2 study is testing the addition of palbociclib (Ibrance, Pfizer) to combined androgen deprivation (NCT02059213).

Cautions

One major concern with molecular phenotyping of mCRPC is the need for invasive biopsies. Though the West and East Coast Dream Teams have achieved 75% to 80% success rates with bone biopsies, others have found an incomplete yield even in experienced test centers, and these tests cause significant discomfort. Of note, the incidence of lymph node involvement appears to have increased over the past 3 decades, which is often easy to biopsy with minimal risk.³⁶ Perhaps just as important is the increasing sophistication and availability of “liquid biopsy” analysis. Many of the assays described above

rely on phenotypes obtained from CTCs or cell-free DNA,^{7,11,13,14} and these techniques offer noninvasive alternatives to bone biopsies.

Though phenotype-driven therapy shows much promise for advanced prostate cancer, it needs to be acknowledged that it is still in an early phase, and there is a valid criticism that these molecular tests have not yet undergone clinical qualification. Perhaps most importantly, we must not waste this opportunity to apply what we learn from our patients. In the current era of extensive molecular phenotyping, it is simply not feasible for every single molecular test to undergo formal clinical qualification as traditionally envisioned. Therefore, the importance of emerging tools to help track and analyze gene-drug interaction data cannot be emphasized enough. Use of CancerLinQ from the American Society of Clinical Oncology, Moffitt Total Cancer Care,³⁷ and other tools, and participation in trials such as TAPUR (Targeted Agent and Profiling Utilization Registry) and NCI-MATCH (NCI-Molecular Analysis for Therapy Choice Program), will help lead to the necessary biomarker qualification. For example, if AR-V7 analysis and subsequent clinical response to various agents were recorded, especially if the Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP)-certified assay utilized to assess alterations were appropriately coded in the database, it should be possible to rapidly determine the utility of the assay in clinical practice.

Conclusion

The increasing clinical use of molecular phenotyping for mCRPC in general, and atypical presentation specifically, can have important value not only to individual patients but also to the field in general. If we continue to investigate the phenotypes underlying our patients' individual cancers, and if we pool our knowledge, we can quickly identify rare cancers that do not represent classic adenocarcinoma, molecularly define the different clinical phenotypes, and begin to generate the data necessary for formal qualification of important biomarkers.

Disclosures

Drs VenderWeele and Stadler have no relevant disclosures.

References

- Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* 1941;1(4):293-297.
- Robinson D, Van Allen EM, Wu Y-M, et al. Integrative clinical genomics of advanced prostate cancer. *Cell.* 2015;161(5):1215-1228.
- Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res.* 2008;68(13):5469-5477.

4. Joseph JD, Lu N, Qian J, et al. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. *Cancer Discov.* 2013;3(9):1020-1029.
5. Korpai M, Korn JM, Gao X, et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov.* 2013;3(9):1030-1043.
6. Mostaghel EA, Marck BT, Plymate SR, et al. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. *Clin Cancer Res.* 2011;17(18):5913-5925.
7. Reyes EE, VanderWeele DJ, Isikbay M, et al. Quantitative characterization of androgen receptor protein expression and cellular localization in circulating tumor cells from patients with metastatic castration-resistant prostate cancer. *J Transl Med.* 2014;12(1):313.
8. Arora VK, Schenkein E, Murali R, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell.* 2013;155(6):1309-1322.
9. Isikbay M, Otto K, Kregel S, et al. Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. *Horm Cancer.* 2014;5(2):72-89.
10. Carver BS, Chapinski C, Wongvipat J, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell.* 2011;19(5):575-586.
11. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med.* 2014;371(11):1028-1038.
12. Zhu M-L, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res.* 2010;70(20):7992-8002.
13. Antonarakis ES, Lu C, Chen Y, et al. AR splice variant 7 (AR-V7) and response to taxanes in men with metastatic castration-resistant prostate cancer (mCRPC) [ASCO abstract 138]. *J Clin Oncol.* 2015;33(7)(suppl).
14. Scher HI, Louw J, Jendrisak A, et al. Predictive biomarkers of sensitivity to androgen receptor signaling (ARS) and taxane-based chemotherapy in circulating tumor cells (CTCs) of patients (pts) with metastatic castration resistant prostate cancer (mCRPC) [ASCO abstract 147]. *J Clin Oncol.* 2015;33(7)(suppl).
15. Small EJ, Huang J, Youngren J, et al. Characterization of neuroendocrine prostate cancer (NEPC) in patients with metastatic castration resistant prostate cancer (mCRPC) resistant to abiraterone (Abi) or enzalutamide (Enz): preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDDT) [ASCO abstract 5003]. *J Clin Oncol.* 2015;33(15)(suppl).
16. Beltran H, Prandi D, Mosquera JM, et al. Defining a molecular subclass of treatment resistant prostate cancer [ASCO abstract 5004]. *J Clin Oncol.* 2015;33(15)(suppl).
17. Beltran H, Rickman DS, Park K, et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discov.* 2011;1(6):487-495.
18. Grasso CS, Wu Y-M, Robinson DR, et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature.* 2012;487(7406):239-243.
19. Baca SC, Prandi D, Lawrence MS, et al. Punctuated evolution of prostate cancer genomes. *Cell.* 2013;153(3):666-677.
20. Haffner MC, Mosbrugger T, Esopi DM, et al. Tracking the clonal origin of lethal prostate cancer. *J Clin Invest.* 2013;123(11):4918-4922.
21. Taylor BS, Schultz N, Hieronymus H, et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell.* 2010;18(1):11-22.
22. Schwartz S, Wongvipat J, Trigwell CB, et al. Feedback suppression of PI3K α signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3K β . *Cancer Cell.* 2015;27(1):109-122.
23. Tryggvadóttir L, Vidarsdóttir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst.* 2007;99(12):929-935.
24. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol.* 2013;31(14):1748-1757.
25. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.* 2015;33(3):244-250.
26. Sandhu SK, Omlin A, Hylands L, et al. Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced germline BRCA2 mutant prostate cancer. *Ann Oncol.* 2013;24(5):1416-1418.
27. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med.* 2009;361(2):123-134.
28. Mateo J, Hall E, Sandhu S, et al. Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial [ESMO abstract LBA20]. *Ann Oncol.* 2014;25(suppl 5).
29. Mateo J, Sandhu S, Miranda S, et al. DNA repair defects and antitumor activity with PARP inhibition: TOPARP, a phase II trial of olaparib in metastatic castration resistant prostate cancer. In: Proceedings from the 106th Annual Meeting of the American Association for Cancer Research; April 18-22, 2015; Philadelphia, PA. Abstract CT322.
30. Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science.* 2005;310(5748):644-648.
31. Brenner JC, Ateeq B, Li Y, et al. Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in ETS gene fusion-positive prostate cancer. *Cancer Cell.* 2011;19(5):664-678.
32. Beltran H, Sboner A, Mosquera JM, et al. Precision medicine program for whole-exome sequencing (WES) provides new insight on platinum sensitivity in advanced prostate cancer (PCa) [ASCO abstract 158]. *J Clin Oncol.* 2015;33(7)(suppl).
33. Palanisamy N, Ateeq B, Kalyana-Sundaram S, et al. Rearrangements of the RAF kinase pathway in prostate cancer, gastric cancer and melanoma. *Nat Med.* 2010;16(7):793-798.
34. Liu J, Pan S, Hsieh MH, et al. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. *Proc Natl Acad Sci U S A.* 2013;110(50):20224-20229.
35. Comstock CES, Augello MA, Goodwin JF, et al. Targeting cell cycle and hormone receptor pathways in cancer. *Oncogene.* 2013;32(48):5481-5491.
36. Doctor SM, Tsao C-K, Godbold JH, Galsky MD, Oh WK. Is prostate cancer changing?: evolving patterns of metastatic castration-resistant prostate cancer. *Cancer.* 2014;120(6):833-839.
37. Fenstermacher DA, Wenham RM, Rollison DE, Dalton WS. Implementing personalized medicine in a cancer center. *Cancer J.* 2011;17(6):528-536.

(continued from page 580)

There Is No Current Role for Molecular Phenotyping in Metastatic Castrate-Resistant Prostate Cancer (cont)

different populations in response to the pressure of AR inhibition, taxanes, and other chemotherapy regimens. Dealing with that horde of clones is a current conundrum because we do not know how to treat the various populations.

A second impediment to molecular phenotyping is the access factor, given that no easy way exists to biopsy all the tumor sites. We certainly do not want to take biopsy samples from dozens of lymph nodes, or dozens of locations in various bones. The presence of heterogeneity means that a biopsy based on one site would not necessarily correlate with findings from another site. Molecular phenotyping has the potential to lead to more biopsies, which are painful and carry a risk of infection.

A third impediment to molecular phenotyping is the fact that we do not have a clear idea about which driver mutations are present in the castration-resistant population. For example, although there is some evidence that the AR-V7 splice variant may predict benefit or lack thereof from abiraterone or enzalutamide, as shown by Antonarakis in the *New England Journal of Medicine*,⁶ it does not appear to be a marker for sensitivity to taxane-based chemotherapy.⁷

The Rationales for Molecular Phenotyping

Of course, there are good rationales for molecular phenotyping. We know that between 20% and 30% of patients with CRPC completely lose the AR driver, or phenotype. Dr Ana Aparicio and her team at MD Anderson published findings in *Clinical Cancer Research* in 2012 and 2013 showing that after 1 or 2 lines of chemotherapy, 20% to 30% of prostate cancers had no evidence of AR expression—they became completely independent of any androgen inhibition.^{8,9} That has led some of us to think that lifelong AR inhibition with leuprolide (Lupron, Abbvie) should be reconsidered. If a patient's tumor becomes fully androgen independent, the corollary that follows is that there is no longer a need for testosterone depletion. The omission of testosterone depletion would vastly improve the quality of life of elderly men who are profoundly hypogonadal.

The development of a simple test to determine whether all of the cancer cells are AR-independent would be a major advance, but there is no easy way to do that right now. One method is the use of CTC assays.

For example, the Cellsearch CTC kit (Janssen Diagnostics) is FDA-approved, and has been shown to be both prognostic and predictive. In 2014, my colleagues and I published data that validated the prognostic role of CTCs

based on the SWOG (Southwest Oncology Group) S0421 trial, a large docetaxel-based prospective cohort. We found that although CTC counts were not a specific molecular marker, they served as a cytopathologic marker for adverse outcome, and a reliable marker for predicting benefit or lack thereof to taxane-based chemotherapy.¹⁰

Unfortunately, this assay is not widely used. Why are we failing to use that marker right now? Of course, there are reimbursement challenges. Another problem is that many physicians view it as a futile test; you do it and then what? I believe that this is a pessimistic approach. I prefer to use the test, and then act on it if I can. I would also like to someday see molecular phenotyping refined and used in conjunction with a CTC assay.

In addition, MYC and P53 are often overexpressed in circulating cells from prostate tumors. Unfortunately, neither of those 2 molecular abnormalities is targetable by anything

A second impediment to molecular phenotyping is the access factor.

other than standard chemotherapy. For this reason, I commonly use gemcitabine and cisplatin in my heavily refractory patients. Chemotherapy has a role to play in highly proliferative malignancies such as Burkitt's lymphoma, which overexpresses MYC, and in *TP53*-mutant cancers.

Other patients who stand to benefit from molecular phenotyping, at least in theory, are those with Lynch syndrome or mismatch repair deficiency. According to a recent paper in the *New England Journal of Medicine*,¹¹ a large percentage of such patients are sensitive to checkpoint inhibition. This study found that colorectal cancer tumors with mismatch repair deficiency but not wild-type tumors had an especially high response rate to pembrolizumab (Keytruda, Merck). There is some possibility that this observation will apply to prostate cancer as well if the prostate cancer arises in a patient with germline mismatch repair deficiency syndrome.

We also have come to learn in recent years that overexpression of the PARP enzyme is common in patients with *BRCA* mutations. The PARP inhibitor olaparib (Lynparza, AstraZeneca) is an active agent in certain patients with prostate cancer. If we perform molecular

phenotype testing and discover a *BRCA* mutation, we suspect that the patient would be sensitive to a PARP inhibitor, based on work by Dr de Bono and colleagues at the Royal Marsden Hospital in London.¹²

Other Alternatives to Molecular Phenotyping

Given the lack of viable biopsy options for molecular phenotyping, our first step is to begin to utilize CTC assays in a more consistent and logical way. AR amplification and potential AR mutations or splice variants such as AR-V7 can easily be identified in CTCs, as can MYC amplification.

A second step is the use of cell-free DNA analysis in plasma. I have been following a few patients using the Guardant360 assay (Guardant Health). This is a blood-based liquid biopsy that analyzes circulating tumor DNA and is currently being marketed for monitoring of lung cancer and epidermal growth factor receptor mutation analysis over time.

A third step should be to perform exploratory work comparing biopsies and CTC data with cell-free DNA data and mutation load. In this way, I think we will gradually dissect out the various molecular subtypes of CRPC, such as the PARP-sensitive *BRCA* mutations. This is going to require concerted effort over protracted periods of time by committed investigators and patients, and by funding agencies that are willing to support what may at times feel a bit like an Easter egg hunt.

The Future

If we do end up using molecular phenotyping, my guess is that we will first of all test for PARP inhibition—that is the low-hanging fruit. PARP deficiencies are present in approximately 5% to 10% of patients, and we already have a drug available to target such individuals. After that, it is unclear what the next step in molecular phenotyping might be.

Disclosures

Dr Vogelzang has served as a consultant to Aveo Pharmaceuticals, Celgene, Dendreon, Exelixis, Janssen Diagnostics, Novartis AG, OncoGeneX/Teva, Veridex, and Viamet. He is a member of the speakers' bureaus for Caris Life Sciences, Eli Lilly, and Sanofi-Aventis.

References

1. Grasso CS, Wu YM, Robinson DR, et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature*. 2012;487(7406):239-243.
2. Morrissey C, Roudier MP, Dowell A, et al. Effects of androgen deprivation therapy and bisphosphonate treatment on bone in patients with metastatic castration-resistant prostate cancer: results from the University of Washington Rapid Autopsy Series. *J Bone Miner Res*. 2013;28(2):333-340.
3. Mehra R, Kumar-Sinha C, Shankar S, et al. Characterization of bone metastases from rapid autopsies of prostate cancer patients. *Clin Cancer Res*. 2011;17(12):3924-3932.
4. Small EJ, Huang J, Youngren J, et al. Characterization of neuroendocrine prostate cancer (NEPC) in patients with metastatic castration resistant prostate cancer (mCRPC) resistant to abiraterone (Abi) or enzalutamide (Enz): preliminary results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team (WCDDT) [ASCO abstract 5003]. *J Clin Oncol*. 2015;33(15)(suppl).
5. Beltran H, Prandi D, Mosquera JM, et al. Defining a molecular subclass of treatment resistant prostate cancer [ASCO abstract 5004]. *J Clin Oncol*. 2015;33(15)(suppl).
6. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014;371(11):1028-1038.
7. Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer [published online June 4, 2015]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.1341.
8. Tzelepi V, Zhang J, Lu JF, et al. Modeling a lethal prostate cancer variant with small-cell carcinoma features. *Clin Cancer Res*. 2012;18(3):666-677.
9. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. *Clin Cancer Res*. 2013;19(13):3621-3630.
10. Goldkorn A, Ely B, Quinn DI, et al. Circulating tumor cell counts are prognostic of overall survival in SWOG S0421: a phase III trial of docetaxel with or without atrasentan for metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2014;32(11):1136-1142.
11. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
12. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123-134.