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Treatment in Intermediate-High Risk Myelofibrosis Patients

BY RICHARD SIMONEAUX

Myelofibrosis is an often-debilitating myeloproliferative disorder that is characterized by symptoms such as enlarged spleen and thrombocytopenia. This presence of thrombocytopenia often serves as an impediment for the use of the dual Janus kinase 1/2 (JAK1/2) inhibitor ruxolitinib. To evaluate the efficacy and safety of the JAK2 inhibitor pacritinib against the best available therapy (BAT) for myelofibrosis, the phase III PERSIST-2 clinical trial was undertaken.

This clinical trial was administered by an international team of clinicians, including Aaron T. Gerds, MD, MS, Assistant Professor of Medicine in the Hematology and Medical Oncology Department at the Cleveland Clinic Taussig Cancer Institute. Recently, a report of study results from this panel was published (*JAMA Oncol* 2018; doi:10.1001/jamaoncol.2017.5818).

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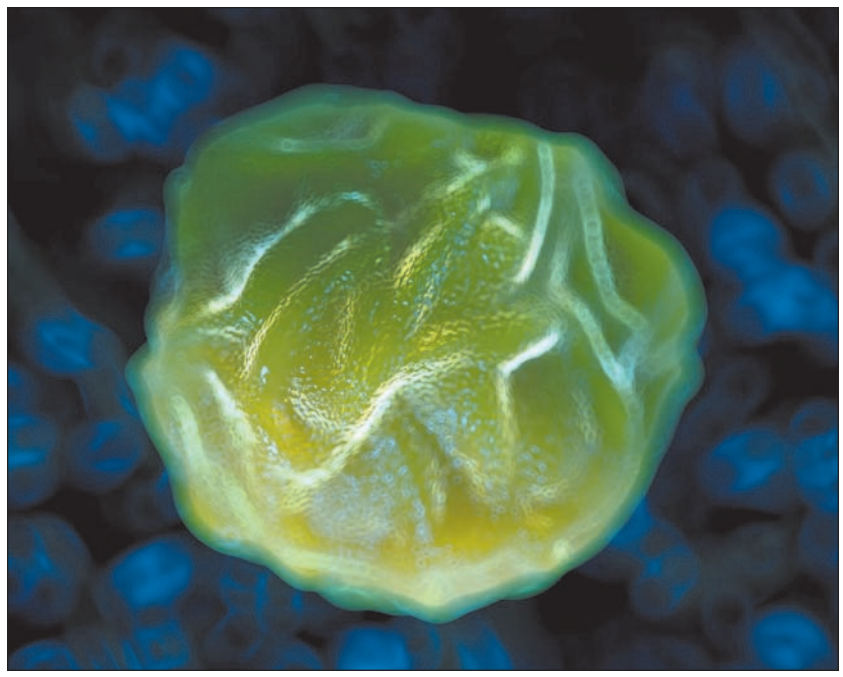

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A Closer Look at the Management of Advanced Testicular Cancer

BY DAVID TOPOLSKY, MD

Testicular germ cell cancer remains one of the most curable solid tumors with an overall survival of over 95 percent. In 2017, there were an estimated 8,850 new cases and 400 deaths resulting from germ cell tumors in the U.S. (*CA Cancer J Clin* 2018;68:7).

Like most solid tumors, initial prognosis and treatment decisions are primarily based on histology and stage. Testicular cancer staging uses the TNM system as well as serum tumor marker status with overall stages ranging from 0 to IIIC (*AJCC Cancer Staging Manuel, Eighth Edition:* Springer, NY:727).

CME Article

Pathologically they are divided into pure seminoma and non-seminomatous germ cell tumors (NSGCT). Based on these two criteria, testicular cancer can be

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NCI Study Revises Molecular Classification for Most Common Lymphoma

In a new study, researchers identified genetic subtypes of diffuse large B-cell lymphoma (DLBCL) that could help explain why some patients with the disease respond to treatment and others don't. The study was led by researchers in the Center for Cancer Research (CCR) at the NCI, with additional authors from several institutions around the world (*N Engl J Med* 2018;378:1396-1407).

"These findings are the culmination of 2 decades of research at NCI and elsewhere, advancing our understanding of the effect of DNA mutations and gene expression on lymphoma biology and outcome," said NCI Director Ned Sharpless, MD. "This refined molecular classification will be instrumental in predicting prognosis and tailoring therapy for patients with DLBCL going forward."

DLBCL is the most common type of lymphoma. Although it can be aggressive, it is potentially curable, and in some patients, treatment eliminates the disease. However, researchers still don't have a full understanding of why some lymphomas of this type respond to treatment and others don't. The standard treatment for the disease is a combination of chemotherapy drugs plus monoclonal antibody rituximab.

Several years ago, researchers defined two major subgroups of DLBCL that arise from different cells of origin and that have different patterns of gene activity. They found that patients with activated B-cell-like (ABC) DLBCL have about a 40 percent average survival rate, while those with germinal center B-cell-like (GCB) DLBCL have

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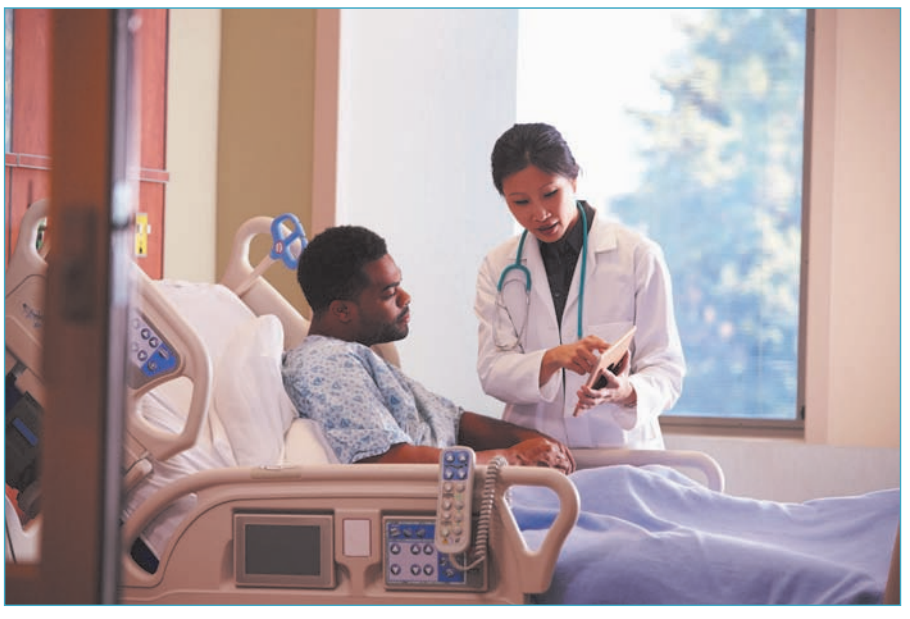
divided into early and advanced groups. Generally speaking, advanced testicular germ cell tumors can be defined as:

- Spread to retroperitoneal nodes (if greater than 2 cm) or any other location (IIb/c or III)
- Persistence of abnormal tumor markers post orchiectomy if cN0M0 (Is)
- Primary mediastinal or retroperitoneal location
- Selected stage IIa seminomas not treated with radiation or IIa NSGCT not treated with retroperitoneal node dissection
- Recurrence following initial cisplatin-based combination chemotherapy

Risk Stratification

Patients who are considered to have advanced disease should then be risk stratified based on the International Germ Cell Cancer Collaborative Group (IGCCCG), which is based on histology (seminoma vs. NSGCT); primary site (testicular/retroperitoneal vs. mediastinal); metastatic sites of involvement (lung and/or nodes vs. other visceral sites); and tumor marker level on day one of systemic therapy and after initial orchiectomy.

This separates advanced seminomas into good and intermediate and NSGCT into good, intermediate, and poor risks groups. This stratification, using clinical data collected from 1975 thru 1990, resulted in distinct prognostic groups with 5-year progression-free survival/overall survival (PFS/OS) of 88/91 percent, 75/79 percent, and 41/48 percent for good, intermediate, and poor risk groups respectively (*J Clin Oncol* 1997;15:594).



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Reassessment of the IGCCCG risk stratification system has been reviewed given the changes in treatment and supportive care over the past 25 years with the recognition that there has been improvement in outcome over that time, especially in the intermediate and poor risk groups (*Ann of Oncol* 2018;29(2):347-351). Investigators are currently evaluating additional prognostic factors to better define the intermediate and poor risk groups, which may lead to different treatment strategies for these patients (*Clin Genitourin Cancer* 2017;15(2):306-312.e3). Under the guidance of the Global Germ Cell Cancer Group, there is a planned IGCCCG update initiative underway.

Indiana University recently reported a reevaluation of the IGCCCG risk stratification using their single institution data from 1998 thru 2014, confirming its ongoing validity noting an improvement in all groups, but was most profound for the intermediate and poor risk groups (*Ann Oncol* 2018;29(2):341-346). Despite this improvement, the poor risk group continued to have a relatively low 5-year PFS/OS of 54/73 percent versus 97/90 percent for the good risk group. It was suggested that the improvement in outcome over the different time frames was a result of multiple factors, including uniform use of cisplatin/etoposide-based chemotherapy, improved supportive care, aggressive post-chemotherapy surgical resection of residual lesions, and treatment at a large volume center with extensive experience with this patient population.

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Systemic Treatment Options

Initial systemic treatment for advanced testicular germ cell cancer patients is primarily determined by the risk stratification status as opposed to histology. Cisplatin-based combination chemotherapy is clearly the treatment of choice for all patients; for good risk patients, bleomycin/etoposide/cisplatin (BEP) or etoposide/cisplatin (EP) are the options almost exclusively used. This was confirmed by Feldman in a MEDLINE and Cochrane Database review which showed at least a 90 percent durable complete response with either three cycles of BEP or four cycles of EP (*JAMA* 2008;299(6):672-684).

For this group of patients we use BEP x three cycles and reserve EP x four cycles for patients with impaired pulmonary function, are at high risk to develop pulmonary symptoms, or who have lifestyles that even small decreases in pulmonary function would be likely to result in a large impact on quality of life.

In intermediate and high-risk patients, it is clear that more aggressive systemic therapy is needed to maximize both disease-free survival (DFS) and OS. BEP remains the most common regimen used, but four cycles as opposed to three are clearly needed (*Eur Urol* 2015;68(6):1054-1068). An alternate regimen of etoposide/ifosfamide/cisplatin (VIP) has also been shown to be effective in this group of patients (*Cancer* 2003;97(8):1869-1875). Like EP in good risk patients, VIP is most commonly used in patients who have a relative contraindication to bleomycin secondary to the presence of, or with a high risk from, developing pulmonary disease.

Because poor risk patients still have a relatively low rate of durable complete responses to either BEP or VIP for four cycles, other treatment options need to be found. The combination of paclitaxel/ifosfamide/cisplatin (TIP) was reported to show an excellent response rate (80% with 68% CR/12% PR negative) and estimated 3-year DFS/OS (72/91%) in intermediate and poor risk patients as first-line therapy (*J Clin Oncol* 2016;34(21);2478-2483). A TIP versus BEP clinical trial is planned (NCT01873326), but is not yet accruing patients.

Another avenue to improve response in these patients is to identify the subset of patients who will not do well with standard BEP x four cycles. The GETUG 13 trial evaluated the rate of tumor marker decline following the first dose of BEP and then randomized those with an unfavorable decline to three additional cycles of BEP versus a dose-dense regimen including paclitaxel, cisplatin, etoposide, oxaliplatin, ifosfamide, and bleomycin. There was an improvement in 5-year PFS but not in OS in this trial (*J Clin Oncol* 2016; doi:10.1200/JCO.2016.34.15_suppl.4504).

Refractory or Relapsed Disease

The other patients in the advanced testicular group are those who have primary cisplatin refractory disease (progression on or relapse within 4 weeks of completion) or relapsed disease (recurrent disease following CR occurring at least 4 weeks post completion of previous treatment). Initial early-stage patients who are chemotherapy-naïve should be treated as described above or considered for retroperitoneal lymph node dissection if appropriate.

Those recurring following previous cisplatin-based therapy should be considered for potentially curative salvage systemic treatment. One option is a second cisplatin containing regime usually using alternate drugs not used in the initial treatment commonly VIP (*J Clin Oncol* 1986;4(4):528-536), TIP (*J Clin Oncol* 2005;23(27):6549-6555), or VeIP (vinblastine/ifosfamide/cisplatin) (*J Clin Oncol* 1998;16(7):2500-2504). The other strategy is high-dose chemotherapy (HDC), usually carboplatin/etoposide and autologous hematopoietic stem cell transplant (HSCT) either up-front or following a variable number of standard-dose cycles of platinum-based therapy.

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TESTICULAR CANCER

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While it is not clear if one of these approaches is superior in relapsed disease, in patients with refractory disease standard-dose chemotherapy is rarely curative. There is only one randomized trial directly comparing standard dose versus HDC and autologous HSCT which did not show a difference in ORR, event-free survival, or 3-year OS in the two arms (*Ann Oncol* 2005;16(7):1152-1159). In this trial, all patients received initial standard-dose chemotherapy and only those that responded were eligible for HSCT.

Lorch, et al (*J Clin Oncol* 2011;29(16):2178-2184), presented a retrospective analysis using an international database from 38 centers including 1,594 patients who were stratified into five prognostic groups from very low to very high risk (*J Clin Oncol* 2010;28(33):4906-4911). Patients totaling 773 received standard-dose chemotherapy and 821 received HDC; there was a statistically significant improvement in PFS and OS in all but the very low risk group noted.

Conversely, a retrospective review of 59 studies reported by Petrelli, et al, which included 1,781 patients treated with standard dose and 2,447 with high-dose therapy failed to show a difference in outcome based on treatment (*Med Oncol* 2017;34(8):133). Currently, the TIGER Trial (NCT02375204), an international collaborative study comparing standard dose combination versus high dose chemotherapy with HSCT in relapsed and refractory germ cell tumors is underway and will hopefully answer this question.

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For patients who do not achieve a CR or relapse following initial salvage the prognosis is poor, with this group accounting for the majority of the deaths secondary to germ cell cancer. These patients are rarely if ever cured so the use of single agent chemotherapy with activity for palliation can be used in patients with poor performance status. Drugs that fit this category include oxaliplatin, gemcitabine, and paclitaxel, which have been reported in phase II trials to have objective response rates of 10-35 percent but with rare complete responses reported. Newer single agent chemotherapies being evaluated include irinotecan and cabazitaxel (*Exp Rev Anticancer Ther* 2018;18(4):389-397).

In patients that continue to have adequate organ function and good performance status combination chemotherapy, most commonly gemcitabine/oxaliplatin/paclitaxel (GOP) has been reported having an objective response rate of 51 percent with an occasional CR (*Ann Oncol* 2008;19(3):448-453). If HSCT has not been utilized, it can be considered in appropriate patients, and in a retrospective study by Einhorn, et al, they did report 45 percent of patients receiving transplant as third-line therapy were disease free during the follow-up period (*N Engl J Med* 2007;357(4):340-348).

New Therapeutic Options Needed

Finally, new and novel agents are needed for this small subset of patients. Several molecularly targeted therapies have been and continue to be evaluated in this setting.

Tyrosine kinase inhibitors and cyclin-dependent kinase inhibition have so far failed to result in meaningful responses (*Exp Rev Anticancer Ther* 2018;18(4):389-397). Interestingly CD30 protein is found on embryonal cells and some seminoma cells. Necchi, et al, presented at ASCO 2016 the preliminary results of a phase II trial of brentuximab vendotin showing high response rates in the first nine patients, but they were of short duration (*J Clin Oncol* 2016; doi:10.1200/jco.2016.34.2_suppl.480).

The first prospective trial of unselected patients given the PD-1 drug pembrolizumab has failed to show any response in 12 patients (*Ann Oncol* 2018;29(1):209-214). Presently there is interest and activity in evaluating other potential targets including EGFR, mTOR, MAPK, RAS, BRAF, MEK, and PARP in this population. OT

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to evaluate treatment options for testicular cancer and examine the pathology and risk stratification of testicular cancer.

GENETIC ROOTS

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to the treatment at all, and researchers didn't understand why. Perhaps a drug was not approved for, say, lung cancer because of such results, but some patients with certain cancer mutations may benefit.

"Most earlier trials were not designed with genomics in mind," Ding said. "We know how these patients responded. Now, we can sequence the tumor samples from patients enrolled in those trials with our latest software tools. We can look for correlations between the patients' genomics and how they responded to the treatments. If we do this for many past trials, we will have tremendous statistical power to identify reasons why drugs work for some patients and not others. So even negative trials that might have been a disappointment at the time can become powerful tools to design better treatments in the future."

In this way, a drug that might have failed as a treatment for lung cancer might be re-examined as a potential therapy for, say, squamous cell carcinoma, again, regardless of location.

In addition to plumbing past studies, Ding said researchers involved with the TCGA project also will begin a new phase of nationwide cancer research called The Human Tumor Atlas, which will include studies of the makeup of the entire tumor, not just cancer cells.

"Even after genomic sequencing, sometimes we still can't explain what is going on," Ding said. "This is why we are planning to expand beyond studies of the tumor cells to include the entire tumor ecosystem—the immune cells that infiltrate the tumor and the supporting tissue that creates the tumor's microenvironment." OT