“You’ll be looking at PD-1 and [ipilimumab] with things like anti-CD137, OX40, [and] other protein checkpoint inhibitors—like Vista, Tim-3, Lag-3, BTLA, CD160, CD244.

There’s a rationale for all these things,” Weber said. Cancer vaccines, kinase inhibitors, and other targeted drugs, and even chemother-apy are other possibilities.

“Obviously you’ve got to prioritize,” Weber said. “But people like me will be kept in business for a long time, testing all these combinations.”

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Overcoming Mantle Cell Lymphoma’s Ibrutinib Resistance

By Gunjan Sinha

A lthough ibrutinib can extend the lives of heavily treated, relapsed, or refractory patients with mantle cell lymphoma (MCL), many become resistant to the drug. A study in September’s Cancer Discovery (2014;4:1022–35) reveals one way that ibrutinib resistance develops and identifies two drugs that may help treat or even prevent it.

“It’s a significant advance,” said Nam Dang, M.D. Ph.D., deputy chief of the division of hematology and oncology at the University of Florida College of Medicine in Gainesville. “Ibrutinib is now becoming widely used,” he added. “By knowing a mechanism of resistance, we can come up with rational strategies to circumvent it.”

Ibrutinib is the first drug to target and inactivate Bruton tyrosine kinase (BTK), which mediates B-cell receptor signaling to enable B cells to survive and proliferate. In November 2013, the U.S. Food and Drug Administration (FDA) approved ibrutinib to treat MCL on the basis of an “unprecedented” response: 68% of patients went into partial or complete remission and the average duration of response was 13.5 months. But most patients eventually relapse.

Selina Chen-Kiang, Ph.D., professor of pathology and laboratory medicine at New York’s Weill Cornell Medical College, and colleagues compared DNA and RNA from normal and tumor cells of patients before, during, and after treatment. BTK genes in tumor cells of patients who developed ibrutinib resistance after responding for at least 14 months had a C481S mutation. Detectable only at relapse, this mutation hindered ibrutinib from binding to BTK.

This mechanism, however, did not explain why about 30% of patients failed to respond to ibrutinib or acquired resistance early. Tumor cells from these patients did not harbor the BTK mutation, suggesting other resistance mechanisms. Further study showed that although ibrutinib did bind to and inactivate BTK, cells expressed high levels of activated PI3K-AKT and cyclin-dependent kinase 4 (CDK4). (PI3K-AKT proteins promote survival; CDK4 drives MCL cells through the cell cycle.) These two mechanisms appeared to override ibrutinib’s inhibitory action in resistant cells, Chen-Kiang said.

“It’s a significant advance. Ibrutinib is now becoming widely used. By knowing a mechanism of resistance, we can come up with rational strategies to circumvent it.”

That discovery suggested two treatment strategies, which the researchers tested in lymphoma cells. In 2004 Chen-Kiang got an experimental selective CDK4/CDK6 inhibitor, now called palbociclib, from Pfizer to study the cell cycle. Her research suggested that the drug might treat blood cancers. In the present study, she and her colleagues killed lymphoma cells expressing the mutated BTKC481S protein. The team administered palbociclib first and then idelalisib—a PI3Kδ inhibitor that FDA approved in July to treat three B-cell blood cancers. The second strategy involved exposing lymphoma cells with normal BTK to palbociclib followed by ibrutinib, which killed the cells. This stepwise drug therapy might treat MCL patients who initially do not respond to ibrutinib, or the drugs given together might prevent resistance.

The team’s approach to understanding and overcoming resistance is laudable, Dang said. “Our approach to combination therapy is often only an educated guess. This paper points us towards a more rational approach.” This study, Chen-Kiang said, is the first to use longitudinal RNA and DNA exome sequencing to study a targeted cancer therapy.

Years ago, research showed that palbociclib might benefit MCL patients. Based on earlier work on lymphoma cell lines, Chen-Kiang persuaded Pfizer in 2007 to sponsor a phase I clinical trial in MCL. Of 17 patients, at least 3 saw their tumors shrink. Meanwhile, other researchers showed the drug to be much better at treating metastatic breast cancer. In August, Pfizer applied for FDA approval of palbo-ciclib plus letrozole as a frontline treatment for postmenopausal women with estrogen receptor–positive, HER2-negative advanced breast cancer.
If FDA approved oncologists could use both idelalisib and palbociclib “off label” to treat MCL.

“But there’s no assurance that what you see in cell lines would be translatable into patients with the same disease,” said George Canellos, M.D., a hematologic oncologist at Boston’s Dana–Farber Cancer Institute. “However, looking at the molecular biology, there are a lot of consistencies between cell lines and patient-derived tissues,” he added.

Chan-Kiang has already launched a clinical trial of ibrutinib plus palbociclib in MCL patients with nonmutated BTK. Meanwhile, “for an MCL patient who has failed ibrutinib and everything else, it would be fair to apply for compassionate use of idelalisib since it’s already approved,” said Robert Hromas, M.D., chair of the department of medicine at the University of Florida College of Medicine.

Payment would be another hurdle, Canellos added. Unless a drug company supplied the drug freely for investigational use or the treatment was part of a clinical trial, insurance companies would probably not cover it.

Chan-Kiang’s study indicates another potential application for idelalisib. FDA has approved it to treat relapsed indolent chronic lymphocytic leukemia, follicular B-cell non-Hodgkin lymphoma, and relapsed small lymphocytic lymphoma. The drug is not indicated for aggressive lymphoma. Working with cell lines, Chan-Kiang and colleagues used palbociclib to turn an aggressive lymphoma into an indolent one and then kill the cells with idelalisib. Researchers are planning a multicenter clinical trial to study the drug combination in aggressive lymphoma patients; Chan-Kiang expects it to launch at the end of this year. (Researchers are also studying ibrutinib to treat indolent chronic lymphocytic leukemia.)

Dysregulation of the CDK4/CDK6 and PK13 pathways is common in human cancers, Chen-Kiang said. She anticipates that drugs that interfere with the cell cycle may be useful in treating different cancers. Moreover, “resistance will be an ongoing problem. We really need to understand how it happens and what we can do to make it better.”

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Home Gardening: An Effective Cancer Therapy

By Mike Fillon

When Joyce Sager learned she had stage I breast cancer, her oncologist recommended she start an exercise program to help her recovery. Once she got over the shock from her diagnosis, Sager joined a gym in Birmingham, Ala. In 5 years, she went only a few times. She felt guilty, but a regimented exercise program and pounding out miles on a treadmill just wasn’t for her.

In summer 2013, someone approached Sager, a high school math teacher, about a program that had recently completed a pilot study. Harvest for Health is an at-home gardening intervention for cancer survivors with a good prognosis and who have completed treatment. What appealed most was that a master gardener (MG) from the Alabama Cooperative Extension System would help Sager set up her garden in containers and raised beds in her own backyard.

“I always wanted to garden, but my previous attempts were miserable failures,” she said.

Wendy Demark-Wahnefried, Ph.D., R.D., Webb Endowed Chair and associate director for cancer prevention and control at the University of Alabama at Birmingham Comprehensive Cancer Center, developed Harvest for Health. The program initially posed one simple question: If cancer survivors started a vegetable garden in their own yard, would they eat more vegetables? To find out, in 2011 she paired 12 adult and child cancer survivors in Jefferson County, Alabama, with MGs. This feasibility study measured how cancer survivors responded to the intervention—how it affected their diet and exercise behaviors, health-related quality of life, biomarkers of successful aging and intestinal health, and physical functioning.

Sager liked that MGs would help her decide what and how to plant, assist with problems such as irrigation and pests, and advise on when and how to harvest. Afterward, her MG would be available for consultations. She signed up and, after doing it for a year, raves about the program.

“One big plus is gardening is more interesting than a gym. Plus, watching my plants grow gives me something to look forward to every day,” she said.

Demark-Wahnefried said that although many studies show links between diet or physical activity and cancer, little is known about how gardening met these requirements. Throughout the yearlong pilot study, the survivor–MG teams planned and planted three gardens for fall, spring, and summer. They harvested and rotated each one, troubleshooting problems. Surveys collected data on diet, physical activity, and quality of life, and the study measured anthropometrics and physical function. A structured debriefing survey was part of the process also.

After 1 year, 40% of participants were eating at least one fruit and vegetable serving per day. Demark-Wahnefried said although increasing fruit and vegetable consumption was the focus, subjects also improved their exercise level. Their physical functioning improved dramatically.

“Our garden drew them outside, they were doing a lot of things around the yard, and maybe taking a walk, and other activities. As a result, the benefit that made this intervention very compelling is their improved physical function,” she said.

Sixty percent of participants engaged in at least 30 minutes of physical activity each week. All improved in three of four...