Chemoprevention
An overview of pharmacologic agents and nursing considerations

Jean E. Boucher, PhD, RN, ANP-BC, AOCNP

Cancer develops from dysplasia of unregulated cells that become malignant, proliferate, and metastasize to other organs and structures. Chemoprevention has been viewed as the optimal strategy to reduce the incidence, morbidity, and mortality of cancer. Chemoprevention consists of primary, secondary, and tertiary strategies, including pharmacologic agents, to prevent the initiation or to slow down the progression of cancer (Landis-Piwowar & Iyer, 2014). Primary chemoprevention agents are administered to the general population with no particular risk factors, secondary chemoprevention agents are prescribed to patients with precancerous malignancies to prevent cancer progression, and tertiary chemoprevention agents are prescribed to prevent recurrent or secondary cancers (Landis-Piwowar & Iyer, 2014). Pharmacologic chemoprevention to prevent or reduce breast, colorectal, prostate, skin, and bladder cancers has been studied for many years. This article provides an update on approved and evolving pharmacologic agents for chemoprevention that are currently being studied.

Pharmacologic Agents
Tamoxifen and raloxifene, selective estrogen receptor modulators (SERMS) approved for chemoprevention by the U.S. Food and Drug Administration (FDA), block estrogen-positive receptors in postmenopausal women for the prevention of tumor growth in patients at risk for or who have breast cancer. Patients on SERMS must be monitored for risks or side effects, which include venous thrombosis and uterine cancer. AIs present less risk but similar concerns. Patients may experience difficulty staying on SERMs and AIs because of intolerable long-term, unwanted side effects, such as arthralgias, hot flashes, myalgias, osteoporosis, and vaginal bleeding (Vogel, 2011).

Clinical trials have shown the benefits of aspirin in people at risk for hereditary colon cancers and in colorectal cancer (CRC) survivors (Burn, Bishop, et al., 2011). The body of robust evidence on the benefits of aspirin to reduce CRC continues to provide the advantages and disadvantages of their use in chemoprevention (Coyle, Cafferty, & Langley, 2016). Aspirin has been shown to be effective for CRC prevention in hereditary nonpolyposis colon cancer or Lynch syndrome (Burn, Bishop, et al., 2011). Aspirin, a nonsteroidal anti-inflammatory drug (NSAID), and cyclooxygenase-2 (COX-2) inhibitors reduce CRC in people with familial adenomatous polyposis (Burn, Gerdes, et al., 2011; Kim & Giardiello, 2011). Widespread use of NSAIDs in the general healthy population has not been recommended because of seminal studies noting risks for bleeding (Chan et al., 2005), as well as cardiovascular events related to COX-2 inhibitors for CRC chemoprevention (Bresalier et al., 2005). Statins, which are used to lower lipid levels (Lochhead & Chan, 2013; Taylor, Wells, & Smolak, 2008), and metformin, which is used to treat type 2 diabetes mellitus (Liu et al., 2017; Zhang et
al., 2011), have also been studied for their ability to inhibit carcinogenesis in patients with CRC. Evidence remains controversial on the benefits, with a study showing inconclusive evidence for statins in preventing CRC (Boudreau, Yu, & Johnson, 2010). Trials on the CRC prevention benefits of metformin in patients with type 2 diabetes mellitus are ongoing. The use of aspirin to reduce the growth of metastases, prevent distant metastases, and decrease the number of cancer deaths continues to be studied (Rothwell et al., 2012).

The preventive benefits of 5-alpha-reductase inhibitors (5-ARIs), particularly finasteride, in prostate cancer have been evaluated in clinical trials (Stephenson, Abouassaly, & Klein, 2010). Two 5-ARIs, finasteride and dutasteride, have not been recommended by the FDA for use in healthy men because of the risk for higher grade tumors (with unknown pathologic mechanisms) and inadequate evidence to reduce mortality (Hamilton & Freedland, 2011). Adverse side effects of 5-ARIs, including sexual dysfunction and mood disorders, also have been noted in men with gynecomasia (Trost, Saitz, & Hellstrom, 2013).

Systemic and topical retinoids, synthetic agents of vitamin A, have been used for decades in chemoprevention of nonmelanoma skin cancers such as actinic keratosis, a precancerous skin lesion (Marquez et al., 2010). Caution in retinoid use has been advised because of birth defects (Browne, Mason, & Tang, 2014). Topical 5-fluorouracil (5-FU), an antimetabolite topical cream and solution, and imiquimod, a synthetic immune response modifier topical cream, have been approved by the FDA for treatment of actinic keratosis and superficial basal cell cancers (Micali, Lacarrubba, Nasca, & Schwartz, 2014). Side effects of these drugs include skin reactions (e.g., blistering, erythema, pruritus). 5-FU should be used cautiously in people with dihydromvertime dehydrogenase deficiency and should not be used by women who may become pregnant (Rogers, Desari, & Eng, 2016).

Agents considered to prevent bladder cancer invasion or recurrence that have been approved by the FDA consist of the bacillus Calmette-Guérin (BCG) vaccine and valrubicin (for BCG refractory carcinoma in situ) in the treatment of bladder dysplasia (Dinney, Greenberg, & Steinberg, 2013; Sylvester, 2011).

The American College of Gastroenterology guidelines recommend the use of proton pump inhibitors, such as omeprazole, in patients with Barrett’s esophagus, a premalignant condition of esophageal cancer, to reduce chronic reflux injury and to control gastrolesophageal reflux disease symptoms (Shaheen, Falk, Iyer, & Gerson, 2016). Avoidance of aspirin and other NSAIDs as an antineoplastic strategy in people with Barrett’s esophagus is also recommended (Shaheen et al., 2016).

### TABLE 1. FDA-APPROVED CHEMOPREVENTION DRUGS

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DRUG AND TARGET DISEASE</th>
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<tbody>
<tr>
<td>Aromatase inhibitor</td>
<td>Anastrozole, exemestane, and letrozole to treat breast cancer</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Valrubicin to treat bladder dysplasia and 5-fluorouracil (Efudex®) to treat superficial basal cell cancer</td>
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<tr>
<td>Epigenic agent</td>
<td>Azacitidine (Vidaza®) and decitabine (Dacogen®), or 5-aza-2’-deoxycytidine, to treat multiple myeloma</td>
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<td>Hepatitis B vaccine</td>
<td>Recombivax HB® to treat hepatocellular cancer</td>
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<tr>
<td>HPV vaccine</td>
<td>HPV 9-valent (Gardasil®) and HPV bivalent (Cervarix®) to treat HPV-related cervical cancer</td>
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<tr>
<td>Immunomodulator</td>
<td>Imiquimod (Aldara®) to treat actinic keratosis</td>
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<tr>
<td>Immunotherapy</td>
<td>Bacillus Calmette-Guérin vaccine to treat bladder dysplasia</td>
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<tr>
<td>Pan-histone deacetylase inhibitor</td>
<td>Vorinostat (suberoylanilide hydroxamic acid) to treat cutaneous T-cell lymphoma</td>
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<tr>
<td>Selective estrogen receptor modulator</td>
<td>Tamoxifen and raloxifene to treat breast cancer</td>
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<tr>
<td>Vitamin A derivative</td>
<td>Retinoids to treat nonmelanoma skin cancers</td>
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</table>

**Note.** Based on information from FDA, n.d.

**OCN® SAMPLE QUESTION**

This is a sample question related to the OCN® examination. Test your knowledge on essential examination content.

Which agent is the most commonly studied chemoprevention to prevent metastases in cancers?
- Aspirin
- Green tea
- Statins
- Synthetic vitamin A

**Answer:** Aspirin

**Additional Considerations**

More rapid evolution of medications in chemoprevention include vaccines and immunomodulators. Two FDA-approved vaccines to prevent human papillomavirus (HPV) are HPV 9-valent (Gardasil®) for HPV types 6, 11, 16, and 18 and HPV bivalent (Cervarix®) for HPV types 16 and 18. Clinical chemoprevention against
hepatocellular cancer after exposure to the hepatitis B virus involves the use of the Recombivax HB® vaccine (Panchal, 2016). Anti-aging agents, such as metformin (antidiabetic agent), resveratrol (stilbenoid found in berries and grapes), and Rhodiola rosea (perennial herbaceous plant), have been linked to anticancer chemoprevention through nutrient-sensing pathways such as insulin-like growth factor 1, mammalian target of rapamycin, adenosine monophosphate-activated protein kinase, and sirtuins (silent information regulator 2 homologs), to promote healthy aging and longevity (Yokoyama, Denmon, Uchio, Jordan, & Mercola, 2015). Dietary and synthetic chemopreventive compounds in clinical trials consist of other phytochemical molecules found in plants, such as apigenin (a bioflavonoid found in grapefruit and chamomile tea that inhibits DNA binding) and curcumin (turmeric) as primary chemoprevention of carcinogenesis (Landis-Piwowar & Iyer, 2014).

Another primary chemoprevention consideration to reverse epigenetic alterations to gene expression (including DNA methylation alteration) is the use of FDA-approved epigenetic drugs vorinostat (suberoylindenide hydroxamic acid) for cutaneous T-cell lymphoma (Mair, Kubicek, & Nijman, 2014) and azacitidine (Vidaza®) and decitabine (Dacogen®) for myelodysplastic syndromes (Landis-Piwowar & Iyer, 2014). The anti-inflammatory suppression properties of Camellia sinensis (green tea) leaves are also being studied in tertiary chemoprevention (Landis-Piwowar & Iyer, 2014).

Oncology nurses need to keep informed of current and newer mechanisms of chemoprevention under study, including many selected molecular targets like chemokines and tumor-blocking, tumor-suppressing, and antiangiogenesis agents (Steward & Brown, 2013). A newer approach for cancer interception in chemoprevention was proposed at the American Association for Cancer Research’s “Shaping the Future of Cancer Prevention: A Roadmap for Integrative Cancer Science and Public Health” summit (Albini, DeCensi, Cavalli, & Costa, 2016), which involves the use of agents to intercept the initiation of carcinogenesis in healthy people within personalized medicine approaches as individualized tailored mechanisms.

**Conclusion**

Patient interest and participation in chemoprevention remains a challenge, with low uptake rates and variation reported in breast cancer chemoprevention in systematic reviews and meta-analyses (Ropka, Keim, & Philbrick, 2010; Smith et al., 2016). Psychological (e.g., mood changes), clinical (e.g., side effects), and demographic factors (e.g., age, comorbidities) must be addressed, including primary care provider knowledge and involvement in treatment decisions.

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