Oral Chemotherapy Agents

NEW ADVANCES IN TARGETED THERAPY, OVERCOMING BARRIERS AND PROMOTING ADHERENCE

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Objectives

- Provide an update on new oral chemotherapy treatments
- Define the role of the oncologist, primary care physician and pharmacist in the management of patients receiving oral chemotherapy
- Address the challenges and barriers to prescribing oral chemotherapy (prior authorization, use of specialty pharmacies, compliance)
<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib</td>
<td>Mekinist®</td>
<td>GSK</td>
<td>Unresectable or metastatic melanoma with BRAF V600</td>
<td>May 2013</td>
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<td>Dabrafenib</td>
<td>Tafinlar®</td>
<td>GSK</td>
<td>Unresectable or metastatic melanoma with BRAF V600</td>
<td>May 2013</td>
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<tr>
<td>Afatinib</td>
<td>Gilotrif®</td>
<td>Boehringer Ingelheim</td>
<td>Metastatic NSCLC with EGFR mutation</td>
<td>July 2013</td>
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<tr>
<td>Ibrutinib</td>
<td>Imbruvica®</td>
<td>Pharmacycics</td>
<td>Mantle Cell Lymphoma; CLL; Waldenstrom’s Macroglobulinemia</td>
<td>Nov 2013; Feb 2014; Jan 2015</td>
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<tr>
<td>Ceritinib</td>
<td>Zykadia®</td>
<td>Novartis</td>
<td>ALK+ metastatic NSCLC</td>
<td>Apr 2014</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Zydelig®</td>
<td>Gilead</td>
<td>Relapsed CLL, follicular B-cell NHL and small lymphocytic lymphoma</td>
<td>July 2014</td>
</tr>
</tbody>
</table>
Changing Landscape

- Traditional Chemotherapy
- Targeted Therapies
  - Monoclonal Antibodies
  - Tyrosine Kinase Inhibitors
  - Hormonal Therapy
  - Immune-Modulating Agents
Tyrosine Kinase Inhibitors (TKI’s)

Diagram showing how growth factors signal to the cell to grow and divide
Copyright © CancerHelp UK

Diagram showing how growth factor inhibitors stop the signal inside the cell
Copyright © CancerHelp UK

Photo Credit: Cancer Research UK
Tyrosine Kinase Inhibitors (TKI’s)

- **Key Characteristics**
  - Small molecules
  - Available for oral administration
  - Undergo first-pass metabolism
  - Highly metabolized by CYP450 enzymes
  - Significant drug interactions
  - Specific administration in relation to meals
  - Unique dosing schedules
  - Unique “on-target” and off-target” toxicities
Clinical Endpoints

- **Overall Survival (OS)**
  - Time from randomization until death from any cause

- **Progression Free Survival (PFS)**
  - Time from randomization until disease progression or death

- **Overall Response Rate (ORR)**
  - Proportion of patients with reduction in tumor burden of a predefined amount

- **Duration of Response (DoR)**
  - Time from documentation of tumor response to disease progression
Melanoma

DABRAFENIB (TAFINLAR®)
TRAMETINIB (MEKINIST®)
Melanoma

- Treatment of metastatic melanoma
  - Traditional drug therapy
    - High-dose IL-2
    - Dacarbazine
    - Biochemotherapy
    - Temozolomide
  - Targeted drug therapy
    - Ipilimumab
    - Vemurafenib
    - Dabrafenib
    - Trametinib
    - Pembrolizumab
    - Nivolumab
Mitogen Activated Protein Kinase (MAPK) Pathway

Photo credit: www.nature.com
Melanoma

- **BRAF mutation**
  - Occurs in about 50% of melanomas
    - BRAF V600E mutation
      - Activates the MAPK pathway
  - Targeted therapy
    - Vemurafenib
    - Dabrafenib
    - Trametinib
Dabrafenib (Tafinlar®)

- **Pharmacology**
  - BRAF TKI

- **Role in Therapy**
  - Unresectable or metastatic melanoma

- **Dosing and Administration**
  - 150 mg PO twice daily on an empty stomach

- **Common Adverse Effects**
  - Skin-related toxicity, fever, fatigue, arthralgia, headache
Clinical Trials

- Phase III study in patients with BRAF V600E mutated metastatic or advanced unresectable melanoma who were randomized to receive dabrafenib or dacarbazine.

- Results
  - PFS
    - 6.9 months dabrafenib vs. 2.7 months dacarbazine (p<0.001)
  - No OS benefit
Trametinib (Mekinist®)

- Pharmacology
  - MEK TKI

- Role in Therapy
  - Unresectable or metastatic melanoma

- Dosing and Administration
  - 2 mg PO once daily on an empty stomach

- Common Adverse Effects
  - Rash, diarrhea, peripheral edema
**Clinical Trials**

- Phase III study in patients with metastatic BRAF V600E or V600K mutation melanoma randomized to receive trametinib or dacarbazine or paclitaxel.
  - Patients could have received one previous chemotherapy regimen in the metastatic setting but not previous treatment with ipilimumab, BRAF inhibitors, or MEK inhibitors

- **Results**
  - PFS 4.8 months trametinib vs. 1.5 months chemotherapy group (p<0.001)
  - OS at 6 months was 81% trametinib group vs. 67% chemotherapy group (p=0.01)
Trametinib (Mekinist®)

• Clinical Trials
  ○ Phase III study in patients with BRAF mutated advanced or metastatic melanoma randomized to receive dabrafenib + trametinib or dabrafenib + placebo
  ○ Results
    ✷ PFS 9.3 months combination group vs. 8.8 months dabrafenib monotherapy (p=0.035)
    ✷ ORR 67% combination group vs. 51% dabrafenib monotherapy (p=0.0015)
    ✷ Interim OS analysis at 9 months showed benefit in combination arm
*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Melanoma

**Bottom line...**
- Dabrafenib + Trametinib is a preferred NCCN regimen (category 1)
  - May be associated with less cutaneous toxicity than monotherapy, but systemic toxicity may be increased
- BRAF inhibitors & MEK inhibitors are associated with a high response rate and responses may be seen in days to weeks of starting the drug
  - But duration of response is low...
- Combination is being explored in the adjuvant setting and in combination with immunotherapy and other new agents
A 45 year old man has metastatic melanoma with metastases to the bone and a BRAF V600E mutation. The patient has been on first-line treatment with dabrafenib 150 mg by mouth twice daily for about 5 months and most recently has developed disease progression. The patient is young and healthy and is willing to try any other treatments that might provide additional benefit. Which one of the following would be best to recommend for this patient?

- A. Add trametinib therapy to dabrafenib
- B. Switch to trametinib
- C. Look at other options besides BRAF inhibitors and MEK inhibitors
- D. Increase the dose of dabrafenib
Non Small Cell Lung Cancer

AFATINIB (GILOTRIF®)
CERITINIB (ZYKADIA®)
Non Small Cell Lung Cancer (NSCLC)

- **Treatment of Stage IV NSCLC**
  - Based on tumor histology and mutation status
    - Targeted therapy
      - Cetuximab
      - Bevacizumab
      - Ramucirumab
    - Tyrosine Kinase Inhibitors
      - Erlotinib
      - Afatinib
      - Crizotinib
      - Ceritinib
    - Systemic chemotherapy
Epidermal Growth Factor Receptor (EGFR) TKI

[Diagram showing the extracellular growth factor binding to the EGFR, leading to activation of PI3K, PTEN, AKT1, mTOR, ERK, and MEK, which in turn regulate cell proliferation, survival, invasion, metastasis, and tumor-induced neoangiogenesis.]
Non Small Cell Lung Cancer (NSCLC)

- Mutations in NSCLC
  - Higher rates observed in women, adenocarcinoma, and never smokers
  - TKI Sensitive
    - Exon 19 deletion
    - Exon 21 substitution
  - TKI Resistant
    - EGFR T790M
      - Acquired resistance to erlotinib
Afatinib (Gilotrif®)

- **Pharmacology**
  - EGFR TKI
    - EGFR, HER2, HER4

- **Role in Therapy**
  - First line treatment of metastatic NSCLC with EGFR mutations including exon 19 deletion or exon 21 substitution mutations
    - Overcomes more drug resistance than erlotinib?

- **Dosing and Administration**
  - 40 mg PO once daily on an empty stomach

- **Common Adverse Effects**
  - Diarrhea, stomatitis, rash/dermatitis, dry skin, paronychia
Clinical Trials

- LUX-Lung study series
  - LUX-Lung 1 (Miller 2012)
    - Phase IIb/III study that included patients who had 1 or 2 prior chemotherapy regimens for metastatic NSCLC with disease progression after at least 12 weeks of treatment of erlotinib or gefitinib
    - Approximately 70% of patients had EGFR mutations
  - Results
    - Median PFS benefit of 3.3 months in the afatinib group vs. 1.1 months with placebo, (p<0.0001)
    - No OS benefit
Afatinib (Gilotrif®)

- **Clinical Trials**
  - LUX-Lung study series
    - LUX-Lung 2 (Yang 2012)
      - Phase II, single-arm study that included patients who had no more than 1 previous chemotherapy regimen and no previous EGFR TKI therapy
      - 82% of patients had an exon 19 deletion or exon 21 substitution mutation with the rest having less common mutations
  - Results
    - ORR = 61%
Afatinib (Gilotrif®)

- **Clinical Trials**
  - LUX-Lung study series
    - LUX-Lung 3 (Sequist 2013)
      - Phase III study of untreated EGFR mutation-positive patients with locally advanced or metastatic NSCLC who were randomized to receive either afatanib or cisplatin and pemetrexed
  - Results
    - Median PFS 11.1 months for the afatinib group vs. 6.9 months for the chemotherapy group (p=0.001)
    - No OS benefit for the afatinib group overall, however significant OS benefit in patients with exon 19 mutation
      - Median OS 33.3 months for the afatinib group vs. 21.1 months for the chemotherapy group
Afatinib (Gilotrif®)

Clinical Trials

- LUX-Lung Study Series
  - LUX-Lung 8 (Goss 2014)
    - Phase III trial in patients with advanced or metastatic squamous cell NSCLC who had failed first line chemotherapy.
    - Patients were randomized to receive either afatinib or erlotinib.
  - Results
    - PFS 2.4 months afatinib vs. 1.9 months erlotinib (p=0.043)
    - ORR not statistically significantly different
    - Safety analysis comparable
Afatinib (Gilotrif®)

- NCCN Guidelines

**SENSITIZING EGFR MUTATION POSITIVE**

**FIRST-LINE THERAPY**

- EGFR mutation discovered prior to first-line chemotherapy
  - Erlotinib (category 1) or Afatinib (category 1)
  - Progression

**SUBSEQUENT THERAPY**

- Asymptomatic
  - Continue erlotinib^mm or afatinib
  - Consider local therapy and continue erlotinib^mm or afatinib

- Symptomatic
  - Isolated lesion
    - Multiple lesions
      - Consider WBRT and continue erlotinib^mm or afatinib
      - Consider local therapy and continue erlotinib^mm or afatinib

- Systemic
  - Multiple lesions
    - Progression, see First-line therapy options for Adenocarcinoma NSCL-19 or Squamous cell carcinoma NSCL-20 ± erlotinib^mm

Photo Credit: www.nccn.org
Afatinib (Gilotrif®)

- **Bottom line...**
  - Both erlotinib and afatinib are Category 1 recommendations per NCCN for EGFR sensitive mutations
    - Erlotinib still used often due to increased experience
    - Different adverse event profiles?
  - Was initially more common to see it used after progression on erlotinib
    - Studies have demonstrated response to afatinib in patients who had progressed on erlotinib and had EGFR mutation positive disease
Anaplastic Lymphoma Kinase (ALK) Inhibitors

Photo Credit: www.nature.com
Anaplastic Lymphoma Kinase (ALK) Inhibitors

- **Mutations in NSCLC**
  - ALK mutation
    - Higher rates observed in adenocarcinoma histology and never smokers
    - Sensitive to ALK inhibitors
      - Crizotinib
      - Ceritinib
Ceritinib (Zykadia®)

- **Pharmacology**
  - ALK TKI and IGF-1 Receptor Inhibitor

- **Role in Therapy**
  - Treatment of patients with ALK-positive metastatic NSCLC who have progressed on or who are intolerant to crizotinib

- **Dosing and Administration**
  - 750 mg PO once daily on an empty stomach

- **Common Adverse Effects**
  - Diarrhea, N/V, abdominal pain, fatigue, anorexia, decreased hemoglobin, hyperglycemia, increased ALT levels
Ceritinib (Zykadia®)

- **Clinical Trials**
  - **Shaw 2014**
    - Phase I study that included 246 patients with metastatic, ALK-positive NSCLC of which 163 patients had progressed on or were intolerant to crizotinib and 66 patients were crizotinib naïve.
    - Dose finding study
      - MTD determined to be 750 mg
    - Results
      - In patients who received Ceritinib > 400 mg per day...
        - Crizotinib-naïve patients – ORR 62%
        - Patients who had progressed on or were intolerant to crizotinib – ORR 56%
        - Stable disease 22%
        - Median PFS 7 months
Ceritinib (Zykadia®)

**Clinical Trials**

- Currently being investigated in two Phase III trials
  - Ceritinib vs. docetaxel or pemetrexed in patients who have previously been treated with chemotherapy and crizotinib
  - Ceritinib vs. standard chemotherapy (pemetrexed with either cisplatin or carboplatin) in first-line treatment of stage IIIb or IV NSCLC
Ceritinib (Zykadia®)

- **Bottom Line...**
  - Use after progression on crizotinib (NCCN category 2A)
  - Results of Phase III trials may move to first-line as alternative to crizotinib

*Category A2*: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
A 62 year old woman with ALK-positive stage IV NSCLC has been receiving crizotinib 250 mg by mouth twice daily and has recently experienced disease progression.

True or False

Ceritinib is not an option for this patient as it has not been shown to have efficacy after failure of other ALK inhibitors.
Hematologic Malignancies

IBRUTINIB (IMBRUVICA®)
IDELALISIB (ZYDELIG®)
Hematologic Malignancies

- Acute Leukemias
- Chronic Leukemias
  - Chronic Lymphocytic Leukemia (CLL)
- Hodgkin’s Lymphoma
- Non-Hodgkin’s Lymphoma
  - Mantle Cell Lymphoma (MCL)
  - Follicular B-cell lymphoma (FL)
  - Waldenström’s macroglobulinemia (WM)
  - Small Lymphocytic Lymphoma (SLL)
- Multiple Myeloma
B-Cell Receptor (BCR) Signaling Pathway

Photo Credit: Seton Hall University College of Arts and Sciences
Ibrutinib (Imbruvica®)

- **Pharmacology**
  - Bruton’s TKI

- **Role in Therapy**
  - Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
  - Treatment of patients with CLL who have received at least one prior therapy or who have 17p deletion
  - Treatment of patients with Waldenström’s macroglobulinemia (WM)

- **Dosing and Administration**
  - MCL: 560 mg PO once daily
  - CLL & WM: 420 mg PO once daily

- **Common Adverse Effects**
  - Thrombocytopenia, neutropenia, anemia, diarrhea, fatigue, musculoskeletal pain, peripheral edema, URTI, N/V, dyspnea, constipation, rash, abdominal pain, decreased appetite
  - Atrial fibrillation, increased bleed risk
Ibrutinib (Imbruvica®)

- Clinical Trials (MCL)
  - Phase II study of previously-treated patients with relapsed or refractory MCL
    - Median number of prior treatments = 3
  - Results
    - ORR 68%
    - DoR 17.5 months
    - PFS 13.9 months
    - OS 58% at 18 months
Ibrutinib (Imbruvica®)

• Clinical Trials (CLL)
  ○ Phase III study of patients with previously treated CLL or SLL randomized to receive either ibrutinib or ofatumumab
    - Median number of prior treatments = 2
    - 32% of patients had 17p deletion
  ○ Results
    - PFS at 9.4 months NR with ibrutinib vs. 8.1 months with ofatumumab
    - OS favorable for ibrutinib
    - ORR 42.6% with ibrutinib vs. 4.1% with ofatumumab (p<0.001)
      ○ Similar results for patients with 17p deletion
Ibrutinib (Imbruvica®)

- **Clinical Trials (WM)**
  - Single-arm study in patients with previously-treated WM
    - Median number of prior treatments = 2
  - Results
    - ORR 61.9%
Phosphatidylinositol 3-Kinase (PI3K) Inhibitor
Idelalisib (Zydelig®)

- **Pharmacology**
  - PI3K Inhibitor

- **Role in Therapy**
  - Treatment of relapsed CLL in combination with rituximab in patients who single-agent rituximab would be considered appropriate therapy due to comorbidities
  - Treatment of relapsed follicular B-cell NHL or relapsed small lymphocytic lymphoma following at least two prior systemic therapies

- **Dosing and Administration**
  - 150 mg PO twice daily

- **Common Adverse Effects**
  - Diarrhea, pyrexia, fatigue, cough, pneumonia, abdominal pain, chills, rash, neutropenia, hypertriglyceridemia, hyperglycemia, AST/ALT elevations
  - Black Box Warnings
    - Hepatoxicity
    - Diarrhea
    - Pneumonitis
    - Intestinal perforation
Idelalisib (Zydelig®)

Clinical Trials (CLL)

- Phase III study during which patients with relapsed CLL who were not eligible to receive chemotherapy due to other comorbidities were randomized to receive either idelalisib and rituximab or placebo and rituximab.

- Results
  - PFS 10.7 months with idelalisib combination vs. 5.5 months with rituximab alone.
  - OS at 12 months was 92% in the idelalisib combination group vs. 80% in the rituximab only group (p=0.02).
Idelalisib (Zydelig®)

- Clinical Trials (FL and small lymphocytic lymphoma)
  - Single-arm, phase II study during which patients with indolent NHL refractory to treatment or who had experienced a relapse 6 months following therapy received idelalisib
  - Previous therapy included rituximab and an alkylating agent
  - Results
    - ORR 57%
    - Median Duration of Response 12.5 months
Hematologic Malignancies

- NCCN Guidelines

NCCN Guidelines Version 2.2015
CLL/SLL

SUGGESTED TREATMENT REGIMENS
(in order of preference)

CLL without del (11q) or del (17p)

- Age ≥70 y and younger patients with significant comorbidities
  - Ibrutinib
  - Idelalisib + rituximab
  - Chemoimmunotherapy
  - Reduced-dose FCR
  - Reduced-dose PCR
  - Bendamustine + rituximab
  - High-dose methylprednisolone (HDMP) + rituximab
  - Rituximab + chlorambucil
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide + rituximab
  - Alemtuzumab + rituximab
  - Dose-dense rituximab (category 2B)

- Age <70 y without significant comorbidities
  - Ibrutinib (category 1)
  - Idelalisib + rituximab
  - Chemoimmunotherapy
  - FCR
  - PCR
  - Bendamustine + rituximab
  - Fludarabine + alemtuzumab
  - RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
  - OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide + rituximab
  - Alemtuzumab + rituximab
  - HDMP + rituximab

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See Supportive Care for Patients with CLL (CSSL-C)
Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

See Suggested Regimens for CLL with del (17p) (3 of 7)
See Suggested Regimens for CLL with del (11q) (4 of 7)

*Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 ml/min or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic...
Hematologic Malignancies

- NCCN Guidelines

NCCN Guidelines Version 2.2015
CLL/SLL

SUGGESTED TREATMENT REGIMENS
(in order of preference)
CLL with del (17p)

First-line therapy
- Ibrutinib
- HDMP + rituximab
- FCR
- FR
- Obinutuzumab + chlorambucil
- Alemtuzumab ± rituximab

Relapsed/Refractory therapy
- Ibrutinib
- Idelalisib ± rituximab
- HDMP ± rituximab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- Ofatumumab
- OFAR

Photo Credit: www.nccn.org
Idelalisib (Zydelig®)

- **Bottom line...**
  - Appropriate agent selection
    - **Idelalisib**
      - CLL patients receiving rituximab
      - Concurrent tx with blood thinners with hx of Afib
      - Pre-existing renal insufficiency
      - 17p deletion?
    - **Ibrutinib**
      - Abnormal liver function
      - Hx of bowel difficulties
      - Lung issues
      - Monotherapy preferred
Practice Challenges

NAVIGATING THE COMPLEX NEW WORLD OF ORAL CHEMOTHERAPY
Changing Landscape of Oncology Therapy

- More oral agents available
  - 25 – 30% of drugs in oncology pipelines are now oral
  - Largest growth is in targeted therapies
- Oral agents still have high toxicity profile, complex dosing, significant drug interactions, and require close monitoring
### Even More New Oral Chemotherapy Agents

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<thead>
<tr>
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<th>Manufacturer</th>
<th>Indication</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>Olaparib</td>
<td>Lynparza®</td>
<td>Astrazeneca</td>
<td>Previously treated BRCA mutated advanced ovarian cancer</td>
<td>Dec 2014</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Farydak®</td>
<td>Novartis</td>
<td>Multiple Myeloma</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Lenvima®</td>
<td>Eisai</td>
<td>Radioactive iodine-refractory differentiated thyroid cancer</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Ibrance®</td>
<td>Pfizer</td>
<td>Advanced ER+, HER2-breast CA</td>
<td>Feb 2015</td>
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Practice Challenges

- Dispensing challenges
- Efficacy monitoring
- Adverse effects
- Adherence
- Cost and billing
Model of Adherence and Persistence

FIGURE 1. Model of Adherence and Persistence.
## Adult Adherence Rates in Oncology Trials

<table>
<thead>
<tr>
<th>YEAR</th>
<th>CANCER</th>
<th>NO.</th>
<th>ORAL THERAPY</th>
<th>ADHERENCE OR PERSISTENCE MEASURE</th>
<th>ADHERENCE OR PERSISTENCE RATE</th>
<th>TIME PERIOD</th>
<th>STUDY</th>
</tr>
</thead>
</table>
| 1987 | Hematologic malignancy   | 108 | Prednisone and allopurinol     | Serum metabolites                                     | Prednisone: 26.8%  
Allopurinol: 16.8%                                         | 6 mo        | Levine 1987<sup>10</sup>; Richardson 1988 |
| 1990 | Breast cancer             | 51  | Cyclophosphamide and/or prednisone | Self-report that 90-110% taken                        | 53% overall with both drugs                            | 6 mo        | Lebovits 1990<sup>21</sup> |
| 1992 | Lymphoma                 | 21  | Chlorambucil, prednisolone, or dexamethasone | Microelectronic monitoring system (MEMS) | 100% (standard deviation [SD]: 20.6%) | 852 d       | Lee 1992<sup>32</sup>   |
| 1993 | Breast cancer             | 26  | Tamoxifen                      | Self-report  
Pill count  
MEMS                                  | 97.9% (SD: 3%) by self-report;  
92.1% (SD: 9.8%) by pill counts;  
85.4% (SD: 17.2%) by MEMS                        | Mean of  
2.92 mo                               | Waterhouse 1993<sup>38</sup> |
| 1993 | Small cell lung cancer   | 12  | Etoposide                      | MEMS                                                  | 93.2% (SD: 12%)                                         | 298 d       | Lee 1993<sup>53</sup>   |
| 1996 | Ovarian cancer            | 11  | Aitretamine                    | MEMS                                                  | 97.4% (SD: 6.9%)                                         | 294 d       | Lee 1996<sup>54</sup>   |
| 2000 | Colon cancer              | 57  | Uracl-tegafur                 | Self-report  
Physician interview  
Urine level                               | 94.4% at 3 mo, 94.7% at 1 y by self-report and interview; 94.7% in range by urine testing of 38 patients at various timepoints | 1 y         | Sadahiro 2000<sup>55</sup> |
| 2002 | Breast cancer             | 53  | Tamoxifen                      | Self-report                                            | 76% missed <1 dose per wk                              | 6 mo        | Murthy 2002<sup>56</sup> |
| 2003 | Breast cancer             | 2,378 | Tamoxifen                  | Prescription refill records                            | 77% filled prescriptions that covered at least 80% of doses over the 1st y; 50% did so by 4th y | 4 y         | Partridge 2003<sup>57</sup> |
| 2005 | Breast cancer             | 110 | Tamoxifen                      | Self-report                                            | 88% adherent                                            | Not stated | Grunfeld 2005<sup>58</sup> |
### Adult Adherence Rates in Oncology Trials, Cont’d

<table>
<thead>
<tr>
<th>Year</th>
<th>Disease</th>
<th>Sample Size</th>
<th>Medication</th>
<th>Adherence Method</th>
<th>Adherence Rate</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Myelodysplastic syndrome</td>
<td>90</td>
<td>Topotecan</td>
<td>MEMS</td>
<td>90%</td>
<td>Klein 2006⁵⁹</td>
</tr>
<tr>
<td>2006</td>
<td>Breast cancer</td>
<td>131</td>
<td>Tamoxifen</td>
<td>Self-report</td>
<td>55% reported nonadherence to medication frequently or occasionally</td>
<td>Atkins 2006⁶⁰</td>
</tr>
<tr>
<td>2007</td>
<td>Breast cancer</td>
<td>2,816</td>
<td>Tamoxifen</td>
<td>Prescription refill records</td>
<td>77.9% at 1 y; 64.8% at 3.5 y</td>
<td>Barron 2007⁶¹</td>
</tr>
<tr>
<td>2007</td>
<td>Breast cancer</td>
<td>1,633</td>
<td>Tamoxifen</td>
<td>Clinical notes, audit records, cancer registry data, prescription records</td>
<td>93% median (95% confidence interval, 84-100%)</td>
<td>Thompson 2007⁶²</td>
</tr>
<tr>
<td>2008</td>
<td>Breast cancer</td>
<td>12,391</td>
<td>Anastrozole</td>
<td>Prescription refill records</td>
<td>78-86% of d were covered by filled prescriptions in Year 1; 62-79% of d were covered by filled prescriptions in Year 3</td>
<td>Partridge 2008⁶²</td>
</tr>
<tr>
<td>2008</td>
<td>Breast cancer</td>
<td>161</td>
<td>Capecitabine</td>
<td>MEMS</td>
<td>76% took at least 80% of doses</td>
<td>Partridge 2008⁶³</td>
</tr>
</tbody>
</table>
Signs and Predictors of Poor Adherence

- Missed appointments
- Inadequate follow up
- Poor patient / provider relationship
- Unfilled prescriptions
- Adverse effects from medications
- Medication cost
- Lack of belief in treatment
- Psychologic problems, particularly depression
Interventions to Increase Adherence

- **Increased accessibility to health care**
  - More convenient follow up schedule
  - Access to providers, nurses, pharmacists, behavioral specialists and social workers

- **Improved dosing plan**
  - Simplify schedule
  - Supply pill boxes to organize doses
  - Pill diary
  - Reminders to take medications (apps, alarms, family and caregivers)
    - OnTime RX
    - MedCoach Medication Reminder
    - Dosecast
    - MediRemind

- **Timely side effect management**
  - Patients know what to expect and what action to take!
Educational Interventions to Increase Adherence

- Increase information provided about disease characteristics
- Risks and benefits of treatment
- Proper use of medication
- Physician initiatives
  - Simplify oral regimen
  - Increase patient understanding of disease and participation in decision making
  - Listen to patient
  - Learn about costs and insurance
  - Reinforce adherence
  - Keep abreast of changes
Best Practice Models

- Oral Chemotherapy Clinics
  - Outcomes
    - Decreased rates of adverse effects
    - Decreased nonadherence
    - Decreased drug interactions
    - Decreased medication errors
    - Increased patient satisfaction
  - Models
    - Collaborative Practice Agreements
    - Medication Therapy Management (MTM)
Available upon request