Optimizing Chemotherapy: Concomitant Medication Lists

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Identifying sources of variability in the response to cancer chemotherapy requires knowledge of all variables, including concomitant medications, that can alter the metabolism and pharmacokinetics of chemotherapy. This study investigated the accuracy of the lists of concomitant medications in the charts of cancer patients. Information collated from a questionnaire, patient interview, and the patient’s medical chart was used to obtain validated medication lists. Patients took an average of 4.8 prescription drugs, 1.6 nonprescription drugs, and 1.6 other remedies within the 3 days prior to chemotherapy. Of the concomitant drugs actually taken, the medical records did not report 24% of prescription drugs, 84% of nonprescription drugs, and 83% of other remedies. Electronic medical records (EMRs) were more complete than paper charts, but even these omitted >75% of nonprescription drugs and other remedies. Potential drug interactions were noted in this study. This study documents the extent and complexity of the concomitant drugs taken by patients undergoing chemotherapy and the deficiencies in recording this information in medical charts.

Cancer therapy has acquired a new focus on “personalized medicine.” The variability among patients in the response to standard therapy has led to an increased awareness of genomic polymorphisms that alter drug metabolism.1 In addition, systems biology has elucidated biological networks that play critical roles in the response of the tumor to therapy.2 Genetic variations within the human population and mutations that arise within tumors can alter these networks and the response to therapy. The emphasis on genetics has provided important insights but overlooks the role of concomitant medications as a critical factor in the response to chemotherapy.

Cancer patients often have unrelated medical conditions that require medications. Use of multiple medications is common especially among the elderly, 29% of whom use at least five prescription medications concurrently.3 Concomitant medications can directly interact with chemotherapy drugs, induce drug metabolism pathways, and change the pharmacodynamics of drugs, all of which can alter the effectiveness of the therapy.4 Riechelmann and colleagues analyzed prescription drug use by patients receiving chemotherapy and identified at least one potential drug interaction in 27% of the patients.5 Patients also self-medicate with nonprescription drugs and use alternative remedies.6–8 Previous studies of interactions between self-administered medications and chemotherapy have revealed many potential adverse interactions.9 Vitamins also have been known to produce drug interactions, prompting some to suggest that they be considered drugs.10 In a study of patients on chemotherapy, McCune and colleagues identified 27% of the patients as being at risk of a detrimental interaction between their chemotherapy drugs and the herbs or vitamins they were taking concomitantly.11 Block and Gyllenhaal reviewed the reported effects of herbal medications on induction of CYP450 enzymes that metabolize chemotherapeutic agents and noted several potentially toxic interactions.12 St. John’s wort induces expression of the cytochrome P450 CYP3A, which alters the metabolism of Irinotecan and other drugs.7,13 Goldstein and colleagues reported that in California 85.6% of adults with cancer took dietary supplements.14

Despite documentation of the extensive use of nonprescription drugs and supplements by cancer patients, few studies have been carried out to investigate the inclusion of this information in patients’ medical records. Accurate medication lists are essential in order to avoid known drug interactions. In addition, accurate medication lists for patients enrolled in clinical trials can aid in identifying previously unrecognized drug interactions.15 This study evaluated the accuracy and

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comprehensiveness of medication lists in the charts of patients receiving chemotherapy. Patients were enrolled from clinics that used electronic medical records (EMRs) and those that relied on paper charts.

RESULTS
Patient demographics
A total of 152 patients (77 men and 75 women) of similar racial and age distribution were enrolled in the study (Table 1). In three of the clinics, data were recorded for all patients who were initially invited to participate. In these three clinics, 75% of the eligible male patients and 98% of the eligible female patients agreed to participate. The most common cancers diagnosed in the study patients were ovarian (17%), lung (15%), head and neck (10%), colorectal (9%), breast (8%), uterine (6%), pancreatic (6%), and prostate (5%).

Prescription medications
Medication reconciliation revealed that patients took an average of 5 (range 0–18) different prescription medications in the 3 days prior to receiving chemotherapy, for a total of 732 reports of prescription drug use among 152 patients. Only 588 of the prescription drugs were recorded in the medical record. Therefore, 174 (24%) of the prescription drugs taken by patients were missing from their medical records. The completeness of the prescription medication list varied by clinic, with medical records failing to include 16 to 37% of the prescription drugs. Prescription drug lists for the patients in the two clinics using EMRs included only 69% of the prescription drugs. The percentage of drugs included in the chart that the patients had not taken in the past 3 days (false positives), did not differ significantly between clinics or by use of EMR vs. paper charts. The cluster-adjusted sensitivity and specificity of the EMRs were 0.8231 and 0.9925, respectively; corresponding values for the paper charts were 0.6951 and 0.9923, respectively.

The medical records listed a large number of prescription drugs that the patients were not taking (Table 2). When research staff reconciled the data in the medical record and the questionnaire, they found that the medical records contained prescription drugs that the patient had taken in the past but was no longer taking. In addition, drugs prescribed “as needed” were also included in the medical chart, irrespective of whether they were actually used by the patient. This study focused on drugs that patients had taken in the 3 days prior to commencement of chemotherapy, in order to identify drugs that may alter the response to chemotherapy. Pain medications and nausea medications are often prescribed “as needed” and taken after chemotherapy. We investigated whether the inclusion of this group of medications in our analysis affected the data on the accuracy of the medical records. Medical records contained 392 false positives, that is, instances where the medical record listed a prescription drug, the use of which was not validated. Of these instances, 134 (34%) involved 16 medications for pain and 13 medications for nausea. These same prescription medications also accounted for 42 false negatives; that is, instances where the medical record failed to report the use of the drug within the previous 3 days. Omitting these pain and nausea medications from the analysis did not alter the finding that clinics using EMRs contained significantly more complete lists of concomitant prescription medications than those using paper charts. After omitting these drugs from the analysis, cluster-adjusted sensitivity and specificity of data from EMRs were 0.8415 and 0.9942, respectively, while the corresponding values from paper charts were 0.6951 and 0.9949, respectively.

A parallel analysis of the information reported by the patients on the questionnaire showed that patients failed to report 131 (18%) of the 732 prescription drugs used (Table 3). Women reported more accurate information than men did; women

| Table 1 Demographic profile of patients | Male (%) | Female (%) | Total (%) |
|----------------------------------------|----------|-----------|-----------|
| Number of patients                     | 77 (50.7)| 75 (49.3) | 152 (100.0)|
| Race                                   |          |           |           |
| African-American                       | 18 (11.8)| 20 (13.2) | 38 (25.0) |
| American-Indian                        | 4 (2.6)  | 2 (1.3)   | 6 (3.9)   |
| Asian                                  | 3 (2.0)  | 0 (0.0)   | 3 (2.0)   |
| Caucasian                              | 51 (33.6)| 47 (30.9) | 98 (64.5) |
| Hispanic                               | 0 (0.0)  | 3 (2.0)   | 3 (2.0)   |
| Other                                  | 0 (0.0)  | 1 (0.7)   | 1 (0.7)   |
| Not reported                           | 1 (0.7)  | 2 (1.3)   | 3 (2.0)   |
| Age (years (mean ± SD))                | 59.9 ± 10.7| 59.0 ± 12.5| 59.5 ± 11.6|
| Range (years)                          | 26–84    | 25–83     | 25–84     |
| Median (years)                         | 60       | 59        | 60        |
| Treatment center                       |          |           |           |
| Clinic A                               | 0 (0.0)  | 33 (21.7) | 33 (21.7) |
| Clinic B                               | 27 (17.8)| 15 (9.9)  | 42 (27.6) |
| Clinic C                               | 26 (17.1)| 26 (17.1) | 52 (34.2) |
| Clinic D                               | 24 (15.8)| 1 (0.7)   | 25 (16.4) |

| Table 2 Concomitant medications in electronic medical records (EMR) vs. paper charts | Total no. of drugs | No. accurate in chart (%) | No. incorrect in chart |
|-----------------------------------------------------------------------------------|-------------------|---------------------------|-----------------------|
| Prescription drugs                                                                 |                   |                           |                       |
| EMR                                                                               | 374               | 310 (82.9)                | 195                   |
| Paper MR                                                                          | 358               | 248 (69.3)                | 197                   |
| Nonprescription drugs                                                              |                   |                           |                       |
| EMR                                                                               | 89                | 20 (22.5)                 | 33                    |
| Paper MR                                                                          | 149               | 19 (12.8)                 | 12                    |
| Vitamins, supplements, and other remedies                                          |                   |                           |                       |
| EMR                                                                               | 110               | 27 (24.5)                 | 21                    |
| Paper MR                                                                          | 139               | 16 (11.5)                 | 3                     |

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failed to report 35 (10%) of 358 prescription drugs, whereas the men failed to report 96 (25%) of 374 prescription drugs \((\chi^2 = 31.4; df = 1; P < 0.0001)\). There were 64 instances in which the patient marked a drug on the questionnaire incorrectly (false positives). Women listed 33 prescription drugs incorrectly (9% of the number of validated drugs used), a proportion that did not differ from men (31 incorrect reports, 8% of validated drugs; \(\chi^2 = 0.1371; df = 1; P = 0.7112\). The instructions on the questionnaire asked for information about medications taken within the past 3 days. When asked by the research staff to confirm that they had actually taken all the marked drugs in the past 3 days, patients admitted to marking some drugs that they had not in fact taken in that 3-day time span or marking a drug other than the one they had intended to. The drugs most commonly misreported in this manner were the pain medications oxycodone, aspirin, and ibuprofen, which were misreported eight, five, and five times, respectively. No other drug accounted for >5% of the incorrect reports (false positives). Among the drugs that patients failed to report (false negatives), no single drug accounted for >5% of the total. Cluster-adjusted sensitivity and specificity of patient reports of prescription drug use were 0.8242 and 0.9988, respectively.

Patients on chemotherapy were taking many prescription drugs that alter P450 metabolism. For example, fluoxetine (Prozac), an inhibitor of CYP2C8, was being taken by a patient on a paclitaxel chemotherapy regimen. Fluoxetine inhibits 6-α-hydroxylation of paclitaxel.16,17

### Nonprescription drugs

The study validated a total of 238 instances of nonprescription drug use in the 3 days prior to chemotherapy, only 39 of which were reported in the medical record (Table 2). The medical records failed to report the use of 199 nonprescription drugs (false negatives). The two clinics using EMRs failed to report 72% (28/39) and 82% (41/50) of the nonprescription drugs in their medical records. The two clinics that used paper charts failed to report 83% (65/78) and 92% (65/71) of the nonprescription drugs in their charts. The failure to include nonprescription drugs (false-negative rate), unadjusted for clustering, was higher \((\chi^2 = 3.84; df = 1; P = 0.0500)\) in clinics that used paper charts 87% (130/149) than in those that used EMRs 78% (69/89). The cluster-adjusted sensitivity of the records was 0.2326 in clinics that used EMRs and 0.0743 in clinics that used paper records. The corresponding specificities were 0.9980 and 0.9993, respectively. Across all four clinics, the unadjusted sensitivity and specificity of the records for nonprescription drugs were 0.1639 and 0.9987, respectively.

The questionnaires were the primary source of information regarding nonprescription drugs taken by the patients. Of the 238 validated instances of nonprescription drug use, patients incorrectly reported 8 drugs and failed to report 16 drugs (Table 3). Three patients accounted for six of these errors by marking the wrong formulation of the drug they were taking. The cluster-adjusted sensitivity and specificity of patient reports of nonprescription drug use were 0.9390 and 0.9998, respectively.

Some of the nonprescription drugs taken by the patients in this study induce or inhibit metabolic enzymes. Ibuprofen has been shown to induce many of the P450 enzymes including CYP3A4.18 Cyclophosphamide is metabolized to its active form via CYP3A4, and induction of CYP3A4 may increase the levels of acrolein, the active metabolite of cyclophosphamide.19 One patient receiving cyclophosphamide indicated use of ibuprofen on the questionnaire, but this information was not in the patient’s medical record. As additional CYP active drugs, such as H-2 antagonist and proton pump inhibitors, are made available as nonprescription agents, the potential for these drug interactions could be expected to increase. For example, omeprazole, a known CYP3A4 inhibitor, may increase methotrexate toxicity.20 An additional area of concern with potential drug interactions is the increasing use of oral agents in the treatment of a variety of cancers. Nonprescription products can interfere with the absorption of drugs used in chemotherapy. For example, dasatinib’s area under the curve is decreased by 55–61% when administered along with antacids or famotidine.21,22 We did not identify these drug combinations in our study; however, the use of nonprescription drugs should be carefully monitored in cancer patients taking oral agents.

#### Vitamins, supplements, and other remedies

Researchers verified that the study patients took 249 vitamins, supplements, or other remedies (including botanicals) within the 3 days prior to chemotherapy; of these, only 43 were recorded in the medical record (Table 2). Vitamins (multivitamins or a high dose of a single vitamin) accounted for 105 of these compounds. Minerals, amino acids, and antioxidants accounted for 46 compounds. Green tea and garlic were used by 12 and 10 patients, respectively. Of the 43 items correctly reported in the medical records, 26 were vitamins. The paper charts correctly reported 25% (27 of 110) of the compounds in this category; of these, 60% were vitamins. The paper charts correctly reported only 12% (16 of 139) of the medications in this category \((\chi^2 = 7.30; df = 1; P = 0.0069)\). The cluster-adjusted sensitivity and specificity of the medical records with respect to vitamins, supplements, and other remedies were 0.1727 and 0.9984, respectively. The medical records did not list the use of any supplement by 64 of the 89 patients for whom there was validated evidence of such use.

Patients reported, through questionnaires, 247 instances of the use of vitamins, supplements, and other remedies, 241 of which were validated and 6 of which were incorrectly reported (Table 3). Patient questionnaires failed to report eight items, the use of which were validated. The cluster-adjusted sensitivity and specificity of patient reports gathered through the questionnaires for this category of drugs were 0.9674 and 0.9996, respectively.

#### Table 3 Concomitant medications self-reported by patients

|                          | Total no. of drugs | No. accurate on questionnaire (%) | No. incorrect on questionnaire |
|--------------------------|--------------------|-----------------------------------|------------------------------|
| Prescription drugs       | 732                | 601 (82.1)                        | 64                           |
| Nonprescription drugs    | 238                | 222 (93.3)                        | 8                            |
| Vitamins, supplements,   | 249                | 241 (96.8)                        | 6                            |

\(\chi^2 = 7.30; df = 1; P = 0.0069\).
Sixteen patients were taking high doses of vitamin C; these included one patient treated with cisplatin and one patient treated with methotrexate. The use of high-dose vitamin C by these patients was not included in either of their medical records. Vitamin C is a potent antioxidant and has been shown to reduce the toxicity of doxorubicin, cisplatin, vincristine, methotrexate, and imatinib. Other potent antioxidants taken by patients within the 3 days prior to chemotherapy included high-dose vitamin E, coenzyme Q10, β-carotene, echinacea, grapefruit juice, and soy.

Clinical trials
Of the 152 patients enrolled in this study, 16 were also concurrently enrolled in a clinical trial. Clinical trials require concomitant medication lists to investigate potential drug interactions. However, the accuracy of the medical records for patients in clinical trials did not differ from those who were not enrolled in a clinical trial (Table 4). The percentages of drugs accurately recorded in the medical records of the patients enrolled in a clinical trial vs. those not enrolled in a clinical trial were 78% vs. 76% for prescription drugs, 16% vs. 16% for nonprescription drugs, and 16% vs. 17% for vitamins, supplements, and other remedies.

Multiple medications containing acetaminophen
An analysis of all medications taken by each patient revealed that six patients had taken two or more medications containing acetaminophen in the 3 days prior to chemotherapy. One patient had taken four medications, including prescription Tylenol w/Codeine, Tylenol Arthritis Pain, Robitussin Night Relief, and Tylenol Cold Relief Nighttime. None of the four medications containing acetaminophen was listed in the patient’s medical chart. Dosing information was not collected, and therefore the total dose of acetaminophen taken by the patient is not known.

DISCUSSION
Paper charts recorded only 69% of the prescription drugs taken by the patients. The capture of prescription drug information was significantly higher with EMRs (83%) or with self-report among patients provided with a list of commonly prescribed medications (82%). On the basis of these data, the shift to EMRs throughout the United States will be beneficial in medication reconciliation of prescription drugs. Federal standards and requirements are under development for the EMRs sold by private companies so that, by the target date of 2014, all medical records will be computerized and could be integrated into a national electronic health information network. The current federal standards for the medication list within the EMR require that the prescription drugs be entered using the standardized drug nomenclature RxNorm. Linking the EMRs to pharmacies should further improve the accuracy and completeness of prescription medication lists.

We documented the use of concomitant medications within the 72 h prior to chemotherapy, the optimal time frame for drug interaction. Induction of drug metabolizing enzymes such as cytochrome P450s occurs within 72 h. In addition, questionnaires requiring patient recall of drugs or dietary items within the previous 72 h have been validated.

Among the prescription drugs in this study, 392 were listed in the charts inaccurately. A previous study of medication reconciliation revealed that 70% of the discrepancies between the EMRs and comprehensive medication assessments were the result of medications remaining active in the medication list when the patient was no longer taking them. Inclusion of end dates for an order is one effective method of correcting this source of error.

Only 17% of nonprescription drugs, vitamins, supplements, and other remedies were included in the medication lists in patients’ charts. Health-care providers are dependent on self-reporting by patients for information about the use of these agents. A checklist not only serves as a reminder to the patients regarding the medications they are taking, but also clarifies the definition of medications. On the questionnaire, one patient indicated having received intravenous injections of large doses of vitamin C from an alternative health practitioner. When the research staff asked whether the patient had informed the oncologist, the patient replied, “No, it is just a vitamin.” There is controversy regarding the effect of high doses of antioxidants such as vitamin C on the efficacy of chemotherapy drugs. It is imperative that oncologists be aware of alternative treatments that their patients are receiving.

In this study, EMRs were more accurate than paper charts in reporting the use of nonprescription drugs (23% vs. 18%) and vitamins, supplements, and other remedies (25% vs. 12%). Nonetheless, the percentages of these medications reported in the EMRs were very low. The Federal Regulations for EMRs do not require that medication lists include nonprescription drugs, vitamins, supplements, and other remedies. There is no standardized reporting system for these items that is similar to the RxNorm reporting system for prescription drugs. Failure to include nonprescription drugs and other items in the EMR medication list eliminates the opportunity to detect patients who are at risk of drug interactions and drug overdoses. A complete and accurate list of prescription and nonprescription medications can alert physicians to potential overdoses of acetaminophen and other drugs that are included in the formulations.

### Table 4 Concomitant medications for patients in clinical trials

|                          | Total no. of drugs (no. per patient) | No. accurate in medical record (no. per patient) | No. incorrect in medical record (no. per patient) |
|--------------------------|-------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Prescription drugs**   |                                     |                                               |                                               |
| Clinical trial           | 54 (3.4)                            | 42 (2.6)                                      | 46 (2.9)                                      |
| Not in trial             | 678 (5.0)                           | 516 (3.8)                                     | 346 (2.5)                                     |
| **Nonprescription drugs**|                                     |                                               |                                               |
| Clinical trial           | 25 (1.6)                            | 4 (0.25)                                      | 2 (0.13)                                      |
| Not in trial             | 213 (1.6)                           | 35 (0.26)                                     | 43 (0.32)                                     |
| **Vitamins, supplements, and other remedies** | |                                               |                                               |
| Clinical trial           | 25 (1.6)                            | 4 (0.25)                                      | 0 (0)                                         |
| Not in trial             | 224 (1.6)                           | 39 (0.29)                                     | 24 (0.18)                                     |
of many medications. The high incidence of liver damage resulting from the concomitant use of multiple medications containing acetaminophen was the subject of recent US Food and Drug Administration Advisory Committee meetings. In our study, there was one patient who took four different medications, all containing acetaminophen, within the 3-day period prior to commencing chemotherapy, none of which was listed in the patient’s medical chart. Many chemotherapy drugs are metabolized by the liver, and impaired liver function can alter the pharmacokinetics of these drugs.

Clinical trials of new therapies require lists of concomitant medications. The data in this study revealed that the medication lists in the charts of patients enrolled in clinical trials were no more complete or accurate than the lists in the charts of the general study population. A survey of patients participating in research studies at National Institutes of Health found that one in six patients was taking a herbal product in addition to the prescribed medication. The limited and erroneous information relating to concomitant drug use in the charts of patients, particularly those on clinical trials, reduces the likelihood of detecting drug interactions.

The data in the current study demonstrate that providing patients with lists of the most common nonprescription drugs, vitamins, supplements, and other remedies yields a medication list that is more comprehensive than the information recorded in the medical chart. It is imperative that comprehensive and accurate information be collected on use of medications by patients, both to ensure patient safety and to aid the development of optimal therapy.

METHODS

Data collection. Eligibility criteria for enrollment in the study included: a diagnosis of cancer, treatment with chemotherapy on the same day that the patient enrolled in the study and completed the questionnaire, and the capacity to give informed consent. Eligible patients were identified by the clinic staff. Consecutive eligible patients receiving their scheduled anticancer therapy were informed about the study by trained research staff and invited to participate. Recruitment goals included approximately equal numbers of men and women. All the patients were provided written informed consent prior to entry into the study. Patients were recruited from the Hematology/Oncology Chemotherapy Clinic and the Gynecologic Oncology Clinic at the University of Oklahoma Health Sciences Center in Oklahoma City, OK, the Chemotherapy Clinic at the Veterans Administration (VA) Hospital in Oklahoma City, Oklahoma, and the Outpatient Oncology Center at the University of Illinois Medical Center in Chicago, Illinois. The study and consent forms were approved by the institutional review boards at all three participating institutions.

The patients were asked to complete a paper copy of a previously validated 11-page questionnaire. The questionnaire’s three sections listed the 228 most commonly prescribed medications, the 210 most commonly used nonprescription drugs, and 75 other remedies. The medications were further subdivided into categories according to the ailment for which they were most commonly used. The patients were instructed to check the box next to any medication they had taken in the past 3 days. Space was provided at the end of each of the three sections for the patients to write in medications they were taking that were not listed on the questionnaire. The questionnaire also included demography-related questions (age, race, and sex) and queried whether the patient was enrolled in a clinical trial.

While the patients completed the questionnaire, a research staff member extracted the current list of medications from the patient’s medical record, which was a paper chart in two clinics and an EMR in the other two clinics. The same research staff member obtained the consent of the patients, administered the survey, and abstracted medications from the charts of all patients at the University of Oklahoma Health Sciences Center and the VA hospital in accordance with standardized protocols. The same standardized protocols were used by the research staff in Chicago. Information on the chemotherapy regimen and pre- and postchemotherapy medications was obtained from the medical records and listed separately by the research staff. After the patient completed the questionnaire, the staff member asked about discrepancies between the information the patient had recorded on the questionnaire and the information in the patient’s medical record. In reconciling the two sources of information, researchers produced a validated medication list for each patient. These validated lists were the standard to which the data from the patient questionnaires and the medical records were compared. In all four clinics, the practice is for the physician to enter the list of concomitant medications into the patient’s chart at the time of his or her initial visit to the oncologist. At subsequent visits, a nurse or pharmacist asks the patient whether there has been any change in his/her medications.

Data analysis. For each patient, the validated medication list, data from the questionnaire, and data from the medical record were entered into a database. The sensitivity and specificity of the patient report and of the medical record were calculated separately, with the validated list as the standard. Estimates of sensitivity and specificity were adjusted for clustering (correlation) of responses within individual patients, using generalized estimating equations within a logistic regression model. Sensitivity was modeled as the predicted probability (adjusted for within-patient correlations) that patients (or patients’ medical records) reported using a drug, given that its use was verified. Similarly, cluster-adjusted specificity was modeled as the predicted probability that patients (or their medical records) correctly did not report using a drug, given that the drug’s nonuse was verified. Cluster-adjusted sensitivities and specificities reported for strata, i.e., for men and women, were calculated from separate generalized estimating equations models. Therefore statistical analyses of differences in proportions or false-negative rates were tested using χ² tests that did not account for clustering of reports within patients.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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