HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2013 November 13.

Published in final edited form as:

Clin Pharmacol Ther. 2011 January ; 89(1): 114–119. doi:10.1038/clpt.2010.253.

Optimizing Chemotherapy: Concomitant Medication Lists

Marie H. Hanigan, Ph.D., **Brian L. dela Cruz, B.S.**, **Stacy S. Shord, Pharm.D., BCOP**, **Patrick J. Medina, Pharm.D., BCOP**, **Javid Fazili, M.D.**, and **David M. Thompson, Ph.D.**

The University of Oklahoma Health Sciences Center, Oklahoma City, OK (M.H.H, B.L.D., P.J.M., J.F., D.M.T.); and The University of Illinois at Chicago, Chicago, IL (S.S.S)

Abstract

Identifying sources of variability in the response to cancer chemotherapy requires knowledge of all variables including concomitant medications, which can alter metabolism and pharmacokinetics of chemotherapy. This study investigated the accuracy of concomitant medication lists in the charts of cancer patients. Collated information from a questionnaire, patient interview and patient's medical chart were used to obtain validated medication lists. Patients took an average of 4.8 prescription drugs, 1.6 non-prescription drugs and 1.6 other remedies within three days prior to chemotherapy. Medical records did not report 24% of prescription drugs, 84% of non-prescription drugs and 83% of other remedies. Electronic medical records were more complete than paper charts, but failed to report more than 75% of non-prescription drugs and other remedies. Potential drug interactions were noted. This study documents the extent and complexity of concomitant drugs taken by patients undergoing chemotherapy and the deficiencies in recording this information in medical charts.

Keywords

Chemotherapy; drug interaction; medication reconciliation; medication list; electronic medical records; patient questionnaire

INTRODUCTION

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 variation 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

Corresponding Author: Dr. Marie H. Hanigan, Biomedical Research Center, Room 264, 975 N.E.10th Street, Oklahoma City, OK 73104; Phone: 405-271-3832; FAX 405-271-3758; marie-hanigan@ouhsc.edu.

Address reprint requests to: Dr. Hanigan at The University of Oklahoma Health Sciences Center, Biomedical Research Center Room 264, 975 N.E. 10th Street, Oklahoma City, OK 73104 or at marie-hanigan@ouhsc.edu.

CONFLICT OF INTEREST/DISCLOSURE

None

important insights but overlooks 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 5 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 analyze prescription drug use by patients on chemotherapy and identified at least one potential drug interaction in 27% of patients [5]. Patients also self medicate with non-prescription drugs and use alternative remedies [6,7,8]. Previous studies of interactions between self-administered medications and chemotherapy have revealed many potential adverse interactions [9]. Vitamins also have known drug interactions prompting some to suggest that they be considered drugs [10]. A study of patients on chemotherapy by McCune and colleagues identified 27% of the patients as being at risk of a detrimental interaction between their chemotherapy and the herbs or vitamins [11]. Block and Gyllenhaal reviewed the reported effects of herbal medications on induction of CYP450 enzymes that metabolize chemotherapeutic agents, noting multiple 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 the adults with cancer took dietary supplements [14].

Despite documentation of extensive use of non-prescription drugs and supplements by cancer patients, few studies have been done to investigate the inclusion of this information in patient's medical records. Accurate medication lists are essential 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 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

Patients Demographics

A total of 152 patients were enrolled in the study. The patients included 77 males and 75 females of similar racial and age distribution (Table 1). In three of the clinics data were recorded for the number of patients invited to participate. In those clinics, 75% of the eligible males and 98% of eligible females agreed to participate. The most common cancer diagnosis among the patients enrolled in the study were: ovarian (17%), lung (15%), head and neck (10%), colorectal (9%), breast (8%), uterine (6%), pancreatic (6%) and prostate cancer (5%).

Prescription Medications

Medication reconciliation revealed that patients took an average of 5 (range 0 – 18) different prescription medications in the three days prior to receiving chemotherapy, 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 the patients were missing from their medical records. The completeness of the prescription medication list varied by clinic, with the medical records failing to include 16 to 37% of the prescription drugs.

Prescription drug lists for the patients in the two clinics using EMRs were significantly more complete than those from clinics using paper charts (Table 2). The EMRs contained 83% of the prescription drugs used by the patients while the paper charts included only 69% of the prescription drugs. The percentage of drugs included in the chart that the patients had not taken in the past three days (false positives) did not differ significantly between clinics or by use of EMR versus paper charts. The cluster-adjusted sensitivity and specificity of the EMRs was 0.8231 and 0.9925, while cluster-adjusted sensitivity and specificity of the paper charts was 0.6951 and 0.9923.

The medical records included a large number of prescription drugs that the patient was 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 included in the chart. This study focused on drugs that had used in the past 3 days, in order to identify drugs that may alter 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, instances where the medical record listed a prescription drug the use of which was not validated. Of these instances, 134 (34%) involved sixteen pain medications or thirteen nausea medications. These same prescription pain medications and nausea medications also accounted for 42 false negatives, where the medical record did not report the drug but researchers validated its use within the previous three 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 EMRs were 0.8415 and 0.9942, while the cluster-adjusted sensitivity and specificity of paper charts were 0.6951 and 0.9949.

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 accurately than men; women failed to report 35 (10%) of 358 prescription drugs while men failed to report 96 (25%) of 374 prescription drugs (χ^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 males (31 incorrect reports, 8% of number of validated drugs; χ^2=0.1371; df=1; p=0.7112). The instructions on the questionnaire asked for medications taken within the past three days. When asked by the research staff if they had taken the drug in the past three days, patients admitted to marking on the questionnaire some drugs they had not taken in that three day time span or they had

marked the wrong drug. The drugs most commonly misreported in this manner were the pain medications oxycodone, aspirin and ibuprofen which were misreported 8, 5 and 5 times respectively. No other drug accounted for more than 5% of the incorrect reports (false positives). Among the drugs they failed to report (false negatives) no single drug accounted for more than 5% of the total. Cluster-adjusted sensitivity and specificity of patient reports of prescription drug use was 0.8242 and 0.9988.

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

Non-Prescription Drugs

The study validated a total of 238 instances of non-prescription drug use in the three days prior to chemotherapy, only 39 of which were reported in the medical record (Table 2). The medical records failed to report use of 199 non-prescription drugs [false negatives]. In the two clinics using EMRs, these records failed to report 72% (28/39) and 82% (41/50) of the non-prescription drugs. Medical records in the two clinics that used paper charts failed to report 83% (65/78) and 92% (65/71) of the non-prescription drugs. The failure to include non-prescription drugs (false negative rate), unadjusted for clustering, was higher (χ^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 medical records' cluster-adjusted sensitivity was 0.2326 in clinics that used EMRs and 0.0743 in clinics that used paper records. Corresponding specificities were 0.9980 and 0.9993, respectively. Across all four clinics, the medical record's unadjusted sensitivity and specificity for non-prescription drugs was 0.1639 and 0.9987.

The questionnaires were the primary source of information regarding non-prescription drugs taken by the patients. Of the 238 validated instances of non-prescription 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 non-prescription drug use was 0.9390 and 0.9998.

Some of the non-prescription 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]. A patients 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 non-prescription 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 includes the increasing use of oral agents in the treatment of a variety of cancers. Non-prescription products can interfere with their absorption. For example, dasatinib's AUC is decreased by 55–61% when administered with antacids or famotidine [21,22]. We did not

identify these drug combinations in our study, but the use of non-prescription drugs should be carefully monitored in cancer patients taking oral agents.

Vitamins, Supplements and Other Remedies

Researchers verified that patients took 249 vitamins, supplements and other remedies (including botanicals) within three days prior to chemotherapy, only 43 of which were recorded in the medical record (Table 2). Vitamins (multi-vitamins or high dose of one 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 record 26 were vitamins. The EMRs correctly reported 25% (27 of 110) of the compounds in this category, 60% of which were vitamins. The paper charts correctly reported only 12% (16 of 139) of the medications in this category (χ^2=7.30; df=1; p=0.0069). The medical record's cluster-adjusted sensitivity and specificity for vitamins, supplements and other remedies were 0.1727 and 0.9984. Medical records did not record any supplement use for 64 of the 89 patients for whom such use was validated.

Patients reported, through questionnaires, 247 instances of 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 8 items the use of which was validated. The cluster-adjusted sensitivity and specificity of patient reports, gathered on the questionnaires, for this category of drugs was 0.9674 and 0.9996.

Sixteen patients were taking high doses of vitamin C including one patient treated with cisplatin and one treated with methotrexate. Use of high dose Vitamin C was not included in either medical record. Vitamin C is a potent antioxidant and has been shown to reduce the toxicity of doxorubicin, cisplatin, vincristine, methotrexate, and imatinib [23]. Other potent antioxidants taken by patients within three days of chemotherapy included high dose Vitamin E, Coenzyme Q10, beta-carotene, echinacea, grapefruit juice and soy.

Clinical Trials

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

Multiple Medications Containing Acetaminophen

Analysis of all the medications taken by each patient revealed that 6 patients had taken 2 or more medications containing acetaminophen in the previous three days. One patient had taken 4 medications including prescription Tylenol w/Codeine®, Tylenol Arthritis Pain®, Robitussin Night Relief® and Tylenol Cold Relief Nighttime®. None of the 4 medications

containing acetaminophen were listed in the patient's medical chart. Dosing information was not collected and therefore the total dose of acetaminophen taken by the patient is unknown.

DISCUSSION

Paper charts recorded only 69% of the prescription drugs taken by the patient. 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%). Based on 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 can be integrated into a national electronic health information network [24]. The current federal standards for the medication list within the EMR require that the prescription drugs be entered using the standardized drug nomenclature RxNorm [25,26]. Linking the EMRs to pharmacies should further improve the accuracy and completeness of prescription medication lists.

We documented the use of concomitant medications within 72 hours prior to chemotherapy, the optimal time frame for drug interaction [27]. Induction of drug metabolizing enzymes such as cytochrome P450s occurs within 72 hours [28,29]. In addition, questionnaires requiring patient recall of drugs or dietary items within the previous 72 hours have been validated [30,31].

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 a comprehensive medication assessment, were the result of medications that the patient was no longer taking remaining active in the medication list [32]. Inclusion of end dates for an order is one effective method for correcting this source of error [33].

Only 17% of non-prescription drugs, vitamins, supplements and other remedies were included in the medication lists in patient's charts. Health care providers are dependent on self-reporting by patients for information about patient's use of non-prescription drugs, vitamins, supplements and other remedies. A checklist not only serves as a reminder to the patient regarding the medications they are taking, it also clarifies the definition of medications. One patient indicated on the questionnaire that they 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 like Vitamin C on the effectiveness of chemotherapy drugs [23,34]. It is imperative that oncologists be aware of alternative treatments that their patients receive.

In this study EMRs were more accurate than paper charts in reporting the use of non-prescription drugs (23% vs 18%) and vitamins, supplements and other remedies (25% vs 12%). Nonetheless, the percentage of these medications reported in the EMRs was very low. The Federal Regulations for EMRs do not require that medication lists include non-prescription drugs, vitamins, supplements and other remedies. There is no standardized

reporting system for these items that is similar to RxNorm for prescription drugs. Failure to include non-prescription 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 non-prescription medications can alert physicians to potential overdoses of acetaminophen and other drugs that are included in the formulation of multiple medications. The high incidence of liver damage due to patients using multiple medications containing acetaminophen was the subject of recent FDA Advisory Committee meetings [35]. Our study found one patient took 4 medications containing acetaminophen within a three day period, none of which were 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 [7,36].

Clinical trials of new therapies require lists of concomitant medications. The data in this study found that the medication list in the charts of patients enrolled in clinical trials were no more complete or accurate than list in the charts of the general study population. A survey of patients participating in research studies at NIH found one in six patients taking an herbal product in addition to the prescribed medication [37]. The limited and erroneous information on concomitant drug use in the charts of patients particularly those on clinical trials, reduces the probability of detecting drug interactions [4,8,38].

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

METHODS

Data Collection

Eligibility criteria for enrollment in the study included: cancer diagnosis, treatment with chemotherapy the same day that the patient enrolled in the study and completed the questionnaire, capacity to give informed consent. Eligible patients were identified by the clinic staff. Consecutive eligible patients receiving their scheduled anti-cancer 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 patients 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, the Chemotherapy Clinic the Veterans Administration 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 Board (IRB) at all three participating institutions.

The patients were asked to complete a paper copy of a previously validated 11-page questionnaire [30]. The questionnaire's three sections listed the 228 most commonly prescribed medications, the 210 most commonly used non-prescription 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 three days. Space was provided at the end of each of the three sections for the patients to write in medications they were taking but were not listed on the questionnaire. The questionnaire also included demographic questions (age, race and sex) and asked whether the patient was enrolled in a clinical trial.

While the patient 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 electronic medical record (EMR) in the other two clinics. A single research staff member consented the patients, administered the survey and abstracted medications from the charts of all patients at OUHSC and the VA hospital according to standardized protocols. The same standardized protocols were used by the research staff in Chicago. Information on the chemotherapy regimen and pre- and post-chemotherapy medications were obtained from the medical record and listed separately by the research staff. After the patient completed the questionnaire, the staff member asked about discrepancies between the information the patient recorded on the questionnaire and the information in the patients' 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 fours clinics, concomitant medications are entered into the patient's chart by the physician at the time of their initial visit to the oncologist. At subsequent visits a nurse or pharmacist asks the patient if there has been any change in their medications.

Data Analysis

For each patient the validated medication list, the data from the questionnaire, the data from their medical record were entered into a database. The sensitivity and specificity of patient report and of 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 by using generalized estimating equations (GEE) within a logistic regression model [39]. 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 non-use was verified. Cluster-adjusted sensitivities and specificities reported for strata, ie for men and women, were calculated from separate GEE models. Therefore, statistical analyses of differences in proportions or false negative rates were tested using Chi-square tests that did not account for clustering of reports within patients.

Acknowledgments

Supported by: RO1CA57530 (M.H.H.) from the National Cancer Institute, National Institutes of Health (U.S.A.).

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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
Non-report	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

Clin Pharmacol Ther. Author manuscript; available in PMC 2013 November 13.

Table 2

Concomitant Medications in Electronic Medical Records (EMR) vs Paper Charts

	Total # of Drugs	# Accurate in Chart (%)	# Incorrect in Chart
Prescription Drugs			
EMR	374	310 (82.9)	195
Paper MR	358	248 (69.3)	197
Non-Prescription 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

Table 3

Concomitant Medications Self-Report by Patients

	Total # of Drugs	# Accurate on Questionnaire (%)	# Incorrect on Questionnaire
Prescription Drugs	732	601 (82.1)	64
Non-Prescription Drugs	238	222 (93.3)	8
Vitamins, Supplements and Other Remedies	249	241 (96.8)	6

Table 4

Concomitant Medications for Patients in Clinical Trials

	Total # of Drugs (# per patient)	# Accurate in Medical Record (# per patient)	# Incorrect in Medical Record (# 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)
Non-Prescription 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)