Published in final edited form as:

J Oncol Pharm Pract. 2018 July ; 24(5): 348–353. doi:10.1177/1078155217704989.

Assessment of Adherence and Relative Dose Intensity with Oral Chemotherapy in Oncology Clinical Trials at an Academic Medical Center

Jeff A. Engle¹, Anne M. Traynor², Toby Campbell², Kari B. Wisinski², Noelle LoConte², Glenn Liu², George Wilding³, and Jill M. Kolesar^{1,2,*}

¹University of Wisconsin-Madison School of Pharmacy, Madison, WI, USA

²University of Wisconsin Carbone Comprehensive Cancer Center, Madison, WI, USA

³The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background/Aims—Oral chemotherapy is increasingly utilized leaving the patient responsible for self-administering an often complex regimen where adverse effects are common. Non-adherence and reduced relative dose intensity (RDI) are both associated with poorer outcomes in the community setting but are rarely reported in clinical trials. The purpose of this study is to quantify adherence and RDI in oncology clinical trials and to determine patient and study related factors that influence adherence and RDI.

Methods—Patients were identified from non-industry funded clinical trials conducted between January 1, 2009 and March 31, 2013 at the University of Wisconsin Carbone Cancer Center. Data were extracted from primary research records. Descriptive statistics and linear regression modeling was performed using SAS 9.4.

Results—A total of 17 clinical trials and 266 subjects were included. Mean adherence was greater than 97% for the first 8 cycles. Mean RDI was less than 90% for the first cycle and declined over time. Male gender, a performance status of 1 or 2, metastatic disease, and traveling more than 90 miles to reach the cancer center were associated with higher RDI.

Conclusions—Patients with cancer enrolled in clinical trials are highly adherent but unlikely to achieve protocol specified relative dose intensity. Given that determining the phase II dose is the primary endpoint of phase I trials, incorporating RDI into this determination should be considered.

Keywords

Oral chemotherapy; adherence; relative dose intensity

*Corresponding Author: Jill Kolesar, PharmD, University of Wisconsin Carbone Cancer Center, CSC, Room K4/554, 600 Highland Avenue, Madison, WI 53792, Phone: (608) 262-5549, Fax: (608) 265-8133, jill.kolesar@wisc.edu.

The data was presented in October 2015 at the American College of Clinical Pharmacy Global Conference on Clinical Pharmacy in San Francisco, California.

INTRODUCTION

Oral chemotherapy is common, comprising approximately 25% of approved antineoplastic agents and an even higher percentage of anticancer medications in development (1). Patients typically prefer oral to intravenous chemotherapy (2,3), however, it leaves the patient with responsibility of adhering to an expensive and often complex regimen where side effects are common.

While there is no universally accepted definition of adherence, adherence has been defined by the WHO as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (4). Adherence to oral anticancer agents varies widely ranging from 16-100% in the community setting (5), and non-adherence is associated with poorer outcomes for patients with chronic myeloid leukemia (6) and breast cancer (7,8,9).

Like adherence, relative dose intensity (RDI) (e.g. dose administered over the total time receiving chemotherapy divided by the standard dose intensity specified in the protocol) (10) can impact patient survival and clinical trial outcomes. In patients with early stage breast cancer (11), achieving a RDI ≥ 85% was associated with longer disease free and overall survival, as was achieving an RDI > 90% in lymphoma (12). Similar results have been observed in breast, lung, and ovarian cancer in the metastatic setting although data is conflicting (13).

While both adherence and RDI have been frequently studied in patients managed in routine clinical practice and associated with clinical outcomes, they are infrequently reported in clinical trials. Despite the recommendations for reporting adherence and RDI in manuscripts by the CONSORT group (14,15), adherence to oral chemotherapy was only reported in 20% of articles describing phase III clinical trials evaluated from the highest quality oncology journals (16) and RDI was reported in only 61% of breast cancer clinical trials (17).

Reduced drug exposure, either through non-adherence or reduced RDI in clinical trials are potential sources of bias, which could result in underestimation of adverse effects and efficacy, overestimation of dose intensity, and ultimately limit power (18). Additionally, in phase I trials where the primary endpoint is usually to determine the recommended phase II dose, non-adherence or decreased RDI can limit assessment of the primary study goal. Jardim and colleagues demonstrated that recommended phase II doses of oral targeted therapies were significantly less likely to be the ultimately approved dose than the recommended phase II dose of standard cytotoxic therapy (19).

The primary aims of the study are to quantify adherence and RDI with oral chemotherapy in the setting of oncology clinical trials. The secondary aims are to determine patient and treatment related factors that predict adherence and RDI.

METHODS

Study Population

Patients were identified from non-industry funded clinical trials conducted at the University of Wisconsin Carbone Cancer Center (UWCCC) in patients with solid tumors. Trials included were open to accrual between January 1, 2009 and March 31, 2013 and had oral chemotherapy as the experimental treatment. Trials were excluded if they enrolled less than 5 subjects, the principal investigator of the clinical trial did not agree to participate, or if study records were unavailable. The study protocol and all included trials were approved by the local institutional review board.

Definitions

Adherence was defined as no missed doses, no extra doses taken, or no doses taken in the wrong quantity or at the wrong time. Adherence was assessed by analyzing patient medication diaries and pharmacy pill counts located in the patient study record. Data was recorded in total milligrams per cycle. Adherence rate was calculated by dividing the total milligrams per cycle by the adjusted dose intensity. Adjusted dose intensity was described as provider or protocol specified dose reductions and was recorded in total milligrams per cycle. For example, if a health care provider advised the patient to change the dosing regimen in any way, patients were considered adherent for that day if the new instructions were followed (e.g. patient is originally prescribed 100 mg per day for 28 days but is dose reduced after 14 days to 100 mg every other day, the adjusted dose intensity is 1400 mg + 700 mg = 2100 mg).

Planned dose intensity was calculated based on the protocol specified dose per day and cycle duration specified by the study protocol (e.g. if the protocol dose is 100 mg per day for a 28 day cycle, the planned dose intensity is 2800 mg per cycle). Planned dose intensity was calculated for each cycle. Patient specific dose intensity was the actual amount of medication taken by the patient in a given cycle (e.g. if the patient took 100 mg per day for 28 days, the patient specific dose intensity is 2800 mg per cycle). The RDI is calculated by dividing the patient specific dose intensity by the planned dose intensity and multiplying by 100 (e.g. if the patient was 100% adherent and had no dose reductions, the RDI was 100).

Data Collection

An online (Oncore) clinical trial management database was used to review trial protocols for inclusion. The individual study protocols were reviewed to determine the planned dose intensity of the study, the phase of the study, the method and frequency of adherence assessment, the individual who conducted the adherence assessment, and the number of oral study medications administered. Individual patient research charts were reviewed to determine patient specific covariates including age, gender, ethnicity, distance from cancer center, type of insurance, performance status (PS), disease type, and disease stage as well as the primary study outcomes; RDI and adherence. In addition, best response to therapy, reason for nonadherence, if the patient was non-adherent, and time on study were also recorded.

Analysis

All analysis was conducted using SAS version 9.4. Visual predictive checks and residual plots were used to assess model fit. Continuous variables that were nonlinear were dichotomized at the mean or median. Adherence and dose intensity were reported as milligrams of medication taken over the study time and were summarized in terms of number of observations, means, and standard deviations. A linear mixed effects model with study and disease random intercepts was used to assess patient specific predictors (age, gender, ethnicity, performance status, disease stage, insurance types) and clinical trial predictors (number of study medications, phase of study, type and frequency of assessment) of RDI while controlling for time on study and cycle number. Non-significant predictors were excluded from final models.

RESULTS

A total of 17 clinical trials enrolling 266 subjects were included in this evaluation. Table 1 describes trial characteristics that were included in the analysis. The analysis included 8 (47%) phase I studies, 6 (35%) phase II studies, and 3 (18%) phase III studies. Adherence was most frequently assessed by a study nurse (70%) and most often using a pill diary (88%) at the beginning of each new treatment cycle (82%).

In this study, 55% of subjects were female patients with a mean age of 58 years (SD = 11.9). See Table 1. Subjects were primarily White (96%) with Blacks and Asians also represented. A number of solid tumors were included in this analysis with colorectal cancer (24%), breast cancer (15%), and prostate cancer (7%) being the most common. Most patients (92%) presented with metastatic disease, had an ECOG performance score of either 1 or 2 (64%), and were enrolled in phase I clinical trials (83%).

Adherence and RDI for the first 8 cycles of therapy were calculated and summarized in Table 2. Mean adherence was greater than 99% in cycle 1 and exceeded 97% for the subsequent 7 cycles of therapy. Because adherence was higher than initially expected, a regression analysis to determine patient and study specific factors that predict medication adherence was not performed. The highest mean RDI was 89.4% in cycle 1, and generally declined with subsequent cycles with the lowest RDI at 72.5% during cycle 8. The number of patients included in each cycle decreased over time as patients went off study due to toxicity or progressive disease, therefore patients remaining on study through cycle 8 had both the best responses to therapy and were most tolerant of the study medications.

A regression analysis was performed to assess factors that predict RDI in the first cycle of therapy and is presented in Table 3. In the first cycle of therapy, male gender, good performance status, metastatic disease, and distance greater than 90 miles from the cancer center were all associated with higher RDI. Other potential predictors were not significant and were not included in the final model for Cycle 1 RDI. A second regression model was developed to assess predictors of RDI over all cycles of therapy and is presented in Table 3. Similar to the factors that predicted higher RDI in Cycle 1, male gender, metastatic disease and distance greater than 90 miles from the UWCCC as well as study phase, with individuals on phase I clinical trials more likely to have higher RDI when compared to those

on phase II or III clinical trials. In this model a significant interaction term between performance status and stage was included, and performance status was no longer significant.

DISCUSSION

The mean adherence in oncology clinical trials exceeded 97% for all cycles of therapy, which is higher than typically reported in clinical practice. The difference in adherence rates observed in these clinical trials compared to clinical practice could be related to the adherence enhancing strategies such as pill diaries, pill counts, and frequent assessments of adherence. A recent systematic review evaluating adherence enhancing strategies in cancer patients receiving oral anticancer agents in the community setting demonstrated no clearly effective strategies for enhancing adherence in this patient population, including counseling programs by nurses, pharmacists, or prefills of pill boxes (20). Therefore, keeping a medication diary and bringing medications to appointments for pill counts may be useful strategies for improving adherence in clinical practice. An additional explanation may be that patients enrolled in clinical trials are more likely to have characteristics associated with adherence (social support, lower out of pocket cost of medications, lack of depression, not elderly) (21) or that patients enrolled in clinical trials have different motivations (perceived benefit of the clinical trial or lack of other therapeutic options) than individuals treated in the community.

The mean RDI in the first cycle was 89.4%, and declined to 72.5% by cycle 8. This is consistent with a retrospective analysis of 933 patients from three phase III breast cancer trials, where RDI was only 85.7% (22). Less than half of patients stayed on study for three cycles, going off study most commonly for either disease progression or adverse effects.

The inability of study subjects to achieve study planned dose intensity even in the first cycle is concerning, especially in the phase I setting where the primary aim is to determine the recommended phase II dose. In the phase I setting, dose reductions of up to 25% are usually allowed within a dosing cohort and these dose reductions are not factored into determining the tolerated dose in the cohort. For example, in a dosing cohort of 300mg, patients could be dose reduced to 225mg, continue on study and 300mg would be reported as the tolerable dose. Given that study participants are generally healthier, younger (23), and have higher incomes (24) than non-participants, it seems unlikely these doses are generalizable to the community. Data from a retrospective analysis supports this, where an evaluation of 20,000 patients with metastatic breast cancer treated in community oncology practices found that dose reductions of 15% and RDI less than 85% occurred in 36.5 and 55.5% of patients, respectively (25). Also concerning are studies suggesting progression-free survival and overall survival decrease when RDI decreases by 10-30% (26,27,28). Given how common both dose reductions and delays are in clinical trials and practice, strategies to accurately describe the dose patients in clinical trials is needed. One suggestion is to take into account RDI when recommending a phase II dose.

Consistent predictors of higher RDI included male gender, metastatic disease, and greater distance from UWCCC. Given the flat dosing of most oral agents and the likely larger BMI

of male subjects compared to female subjects it is possible this gender difference is related to drug exposure and suggesting that drug exposure between males and females or by BMI should be assessed and reported in phase I clinical trials. Patients with metastatic disease and traveling a long distance for treatment were likely very motivated to stay on therapy, either because of perceived benefit or lack of other therapeutic options (29,30).

In the model including all cycles, PS was no longer a significant predictor when an interaction term between performance status and disease stage was included. Individuals with either a good performance status and advanced stage disease or a poor performance status and early stage disease were more likely to achieve higher RDI than subjects with a poor performance status and advanced disease or early stage disease and a good performance status, suggesting that advanced stage disease is a motivator to achieve RDI, however ability to achieve RDI is limited by performance status.

Limitations of this study include the retrospective, single institution design and the inability to assess all potentially predictive covariates. The generalizability is also limited, given that the majority of patients had metastatic disease, were enrolled in federally funded clinical trials and there was an over representation of phase I studies. In addition, there was significant drop out at later cycles of therapy, although the predictors of RDI were similar in both cycle 1 and across all cycles, minimizing this concern.

CONCLUSION

Patients with cancer enrolled in clinical trials are highly adherent but unlikely to achieve protocol specified relative dose intensity. Given that determining the phase II dose is the primary endpoint of phase I trials, incorporating RDI into this determination should be considered.

References

1. Bassan F, Peter F, Houbre B, et al. Adherence to oral antineoplastic agents by cancer patients: definition and literature review. *Eur J Cancer Care (Engl)*. 2014; 23:22–35. [PubMed: 24079854]
2. Fallowfield L, Atkins L, Catt S, et al. Patients' preferences for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol*. 2006; 17:205–10. [PubMed: 16239231]
3. Jensen LH, Osterlind K, Rytter C. Randomized cross-over study of patient preference for oral or intravenous vinorelbine in combination with carboplatin in the treatment of advanced NSCLC. *Lung Cancer*. 2008 Oct; 62(1):85–91. [PubMed: 18372075]
4. World Health Organization. Adherence to long-term therapies: Evidence for action. WHO; 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed 2.12.17
5. Foulon V, Schöffski P, Wolter P. Patient adherence to oral anticancer drugs: an emerging issue in modern oncology. *Acta Clin Belg*. 2011; 66(2):85–96. [PubMed: 21630604]
6. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol*. 2010 May; 28(14):10. 2381–88.
7. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer*. 2008; 99(11):1763–68. [PubMed: 18985046]

8. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat.* 2011; 126:529–37. [PubMed: 20803066]
9. Hsieh KP, Chen LC, Cheung KL, et al. Interruption and non-adherence to long-term adjuvant hormone therapy is associated with adverse survival outcome of breast cancer women-an Asian population-based study. *PLoS One.* 2014 Feb 21;9(2):e87027. [PubMed: 24586261]
10. Hryniuk WM. The importance of dose intensity in the outcome of chemotherapy. *Important Adv Oncol.* 1988;121–41. [PubMed: 3042601]
11. Chirivella I, Bermejo B, Insa A, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. *Breast Cancer Res Treat.* 2009; 114(3):479–84. [PubMed: 18463977]
12. Bosly A, Bron D, Van Hoof A, et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. *Ann Hematol.* 2008; 87(4):277–83. [PubMed: 17952688]
13. Brunetto AT, Carden CP, Myerson J, et al. Modest reductions in dose intensity and drug-induced neutropenia have no major impact on survival of patients with non-small cell lung cancer treated with platinum-doublet chemotherapy. *J Thorac Oncol.* 2010; 5(9):1397–403. [PubMed: 20644495]
14. Gossec L, Tubach F, Dougados M, et al. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review. *Am J Med Sci.* 2007; 334:248–54. [PubMed: 18030180]
15. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* 2010; 152(11):726–32. [PubMed: 20335313]
16. Bergsbaken J, Eickhoff J, Buss B, et al. Assessment of adherence with oral anticancer agents in oncology clinical trials: A systematic review. *J Oncol Pharm Pract.* 2016; 22(1):105–13. [PubMed: 25577495]
17. Altwaigi AK, Alfakeeh AH, Hopman WM, et al. Quality of reporting of chemotherapy compliance in randomized controlled trials of breast cancer treatment. *Jpn J Clin Oncol.* 2015 Jun; 45(6):520–6. [PubMed: 26059696]
18. Robiner WN. Enhancing adherence in clinical research. *Contemp Clin Trials.* 2005; 26(1):59–77. [PubMed: 15837453]
19. Jardim DL, Hess KR, Lorusso P, et al. Predictive value of phase I trials for safety in later trials and final approved dose: analysis of 61 approved cancer drugs. *Clin Cancer Res.* 2014 Jan 15; 20(2): 281–8. [PubMed: 24190980]
20. Mathes T, Antoine SL, Pieper D, et al. Adherence enhancing interventions for oral anticancer agents: a systematic review. *Cancer Treat Rev.* 2014 Feb; 40(1):102–8. [PubMed: 23910455]
21. Mathes T, Pieper D, Antoine SL, et al. Adherence influencing factors in patients taking oral anticancer agents: a systematic review. *Cancer Epidemiol.* 2014; 38(3):214–26. [PubMed: 24768601]
22. Loibl S, Skacel T, Nekljudova V, et al. Evaluating the impact of Relative Total Dose Intensity (RTDI) on patients' short and long-term outcome in taxane- and anthracycline-based chemotherapy of metastatic breast cancer- a pooled analysis. *BMC Cancer.* 2011; 11:131. [PubMed: 21486442]
23. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. *Perspect Clin Res.* 2015 Oct-Dec;6(4):184–9. [PubMed: 26623388]
24. Unger JM, Gralow JR, Albain KS, et al. Patient Income Level and Cancer Clinical Trial Participation: A Prospective Survey Study. *JAMA Oncol.* 2016 Jan 1; 2(1):137–9. [PubMed: 26468994]
25. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol.* 2003; 21(24): 4524–31. [PubMed: 14673039]
26. Yuan JQ, Wang SM, Tang LL, et al. Relative dose intensity and therapy efficacy in different breast cancer molecular subtypes: a retrospective study of early stage breast cancer patients treated with neoadjuvant chemotherapy. *Breast Cancer Res Treat.* 2015; 151(2):405–13. [PubMed: 25956059]

27. Bouvet E, Borel C, Obéric L, et al. Impact of dose intensity on outcome of fludarabine, cyclophosphamide, and rituximab regimen given in the first-line therapy for chronic lymphocytic leukemia. *Haematologica*. 2013; 98(1):65–70. [PubMed: 23065520]
28. Aspinall SL, Good CB, Zhao X, et al. Adjuvant chemotherapy for stage III colon cancer: relative dose intensity and survival among veterans. *BMC Cancer*. 2015; 15:62. [PubMed: 25884851]
29. Nipp RD, Lee H, Powell E, et al. Financial Burden of Cancer Clinical Trial Participation and the Impact of a Cancer Care Equity Program. *Oncologist*. 2016 Apr; 21(4):467–74. [PubMed: 26975867]
30. Ulrich CM, Ratcliffe SJ, Wallen GR, et al. Cancer clinical trial participants' assessment of risk and benefit. *AJOB Empir Bioeth*. 2016; 7(1):8–16. Epub 2015 May 1. [PubMed: 26709381]

Table 1

Study and Patient Characteristics

Variable	No.	%
Study Characteristics		
Clinical Trials	17	
Trial Phase		
Phase I	8	47.1
Phase II	6	35.3
Phase III	3	17.6
Number of Oral Chemotherapy Agents		
One	14	82.0
Two	3	18.0
Adherence Assessment Tool		
Pill Diary	15	88.0
Verbal	2	12.0
Frequency of Adherence Assessment		
Each cycle	14	82.0
Each study visit	2	12.0
Annually	1	6.0
Assessor of Adherence		
Study nurse	12	70.0
Treating physician	2	12.0
Study coordinator	2	12.0
Unknown	1	6.0
Patient Demographics		
Age		
65 years	181	68
> 65 years	85	32
Gender		
Male	121	45.5
Female	145	54.5
Race		
White	248	96.1
Other	10	3.9
Patients per Trial Phase		
Phase I	220	82.7
Phase II–III	46	17.3

Variable	No.	%
Number of Oral Chemotherapy Agents		
One	162	60.9
Two	104	39.1
Performance Status		
0	95	35.7
1–2	171	64.3
Type of Cancer		
Colorectal	64	24.1
Breast	42	15.8
Neuroendocrine	27	10.2
Lung	26	9.8
Prostate	18	6.8
Ovarian	11	4.2
Head and Neck	10	3.8
Other	67	25.3
Cancer Stage		
Localized	20	7.6
Metastatic	243	92.4
Distance from Medical Center		
90 miles	194	73
> 90 miles	72	27
Time on Study		
4 months	202	76
> 4 months	64	24
Best Response		
Response (CR, PR, SD)	96	37.1
Progressive Disease	126	48.6
Toxicity	31	12.0
Lost to follow-up	6	2.3

Table 2

Subject Adherence and Relative Dose Intensity Per Cycle

Cycle	No. of Subjects	Mean Adherence	Mean Relative Dose Intensity
		Percent	Percent
1	264	99.2 ± 4.48	89.4 ± 23.6
2	201	99.1 ± 3.02	82.6 ± 23.4
3	101	97.6 ± 7.99	84.0 ± 22.8
4	86	99.0 ± 3.39	78.1 ± 26.3
5	50	97.5 ± 10.8	79.1 ± 24.3
6	45	98.5 ± 4.62	81.3 ± 24.5
7	32	99.8 ± 0.75	86.0 ± 19.6
8	23	99.8 ± 0.74	72.5 ± 26.2

Table 3

Factors Predicting Higher Relative Dose Intensity

Variable	Estimate	95% CI	p-value
Cycle 1			
Male Gender	0.083	0.03–0.15	0.0047
Distance (90 miles) from UWCCC	0.088	0.03–0.14	0.0034
Performance Status (0 vs. 1 or 2)	0.088	0.03–0.14	0.0025
Disease Stage (metastatic versus local)	0.204	0.09–0.32	0.0004
All Cycles *			
Male Gender	0.050	0.02–0.08	0.0027
Distance (90 miles) from UWCCC	0.052	0.02–0.09	0.0041
Performance Status (0 vs 1 or 2)	0.097	0.06–0.13	0.54
Disease Stage (metastatic vs. local)	0.076	0.00–0.16	<0.0001
Trial Phase (I vs. II–III)	0.138	0.07–0.21	<0.0001
Performance Status*Stage	0.238	0.10–0.37	0.0006

* Controlled for time on study and cycle number