Adherence to Oral Chemotherapy in Acute Lymphoblastic Leukemia

Subjects: Oncology

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Acute lymphoblastic leukemia (ALL) is the most common cancer affecting children and adolescents. Medication adherence can be defined as taking medications exactly as prescribed by a medical provider. It includes taking the right medication at the right dose at the right time, consistently.

leukemia lymphoblastic leukemia acute lymphoblastic leukemia

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer affecting children and adolescents [1]. The 5-year survival rate is approaching 90% after treatment with multi-agent chemotherapy [2][3]. Treatment typically lasts 2–3 years, and begins with up to 9 months intensive chemotherapy followed by a prolonged low-intensity maintenance phase that lasts for the remainder of therapy [4]. Maintenance phase is predominated by an oral chemotherapy regimen consisting of daily 6-mercaptopurine (6-MP) or, less commonly, daily 6-thioguanine (6TG), weekly methotrexate (MTX), and intermittent oral steroid bursts, all given at home by patients or caregivers [5]. The long duration of maintenance therapy has been shown to reduce odds of relapse [5]; however, it requires adequate adherence to the prescribed regimen.

Oral chemotherapy has many perceived benefits compared to intravenous (IV) chemotherapy, including greater flexibility, fewer interruptions to usual routines, fewer trips to the hospital, and reduced stress [6][7]. However, administration of medications at home provides new challenges, as the burden of medication administration is shifted from provider to patient. One of the most notable challenges is medication adherence [8]. Medication adherence can be defined as taking medications exactly as prescribed by a medical provider. It includes taking the right medication at the right dose at the right time, consistently [9]. Across oncologic conditions, adherence to oral chemotherapy is a challenge, with widely variable adherence rates of 17–100% [8].

2. Pharmacologic Adherence

2.1. Thiopurines (6-mercaptopurine)

Daily thiopurines, predominantly 6-mercaptopurine (6MP), make up the backbone of maintenance therapy for acute leukemias. Here, 15 of the 28 publications analyzing adherence to thiopurines reported pharmacological measurements of 6MP. Measurements of the thiopurine metabolites (thioguanine nucleotides [TGN] and

methylmercaptopurine [MMP]) were the most reported (*n* = 13) [10][11][12][13][14][15][16][17][18][19][20][21][22]. Direct measures of serum 6MP level [23] and urine 6MP level [24] were reported in one article each. Overall, prevalence of nonadherence to 6MP using pharmacological assessment was widely variable 2–67%. There was no consensus definition of nonadherence. The most common definition of nonadherence was based on low MMP and TGN levels (*n* = 7) which reflected chronic low exposure. However, the cut off values for low were not consistent. Prevalence of overt nonadherence using undetectable metabolite levels was the lowest at 2–3%. Prevalence of partial nonadherence was detected using various definitions, including: metabolite level cut offs in the lower quartile, or less than 20th percentile (10–15%); relative decrease in metabolite level without decrease in medication dose (17%); hierarchical cluster analysis to determine low TGN and low MMP group (21–53%); single metabolite level below therapeutic range (58–67%). Nonadherence was also defined using variability in TGN levels, with prevalence of 5–27%. Use of direct measurements of mercaptopurine, whether in serum or urine, was limited (*n* = 2) due to variable inter-patient pharmacokinetics and rapid drug metabolism.

2.2. Methotrexate

Weekly low-dose methotrexate (MTX) is an integral component of maintenance therapy for ALL. Thus, 3 of the 5 publications reporting prevalence of nonadherence to oral MTX used pharmacological measures, including serum MTX [25], erythrocyte MTX (eMTX) [22], and neutrophil MTX (nMTX) [26]. Like serum measurements of 6MP, MTX levels in serum drop rapidly after drug ingestion and metabolites accumulate intracellularly in erythrocytes and neutrophils. Overall, prevalence of nonadherence to MTX using pharmacological assessment was between 5–29%. All three methods used undetectable level as the definition of nonadherence. Undetectable serum MTX yielded a higher prevalence of nonadherence of 29%, compared to undetectable measurements of intracellular MTX metabolites (eMTX or nMTX) yielding prevalence of 5–6%.

2.3. Steroids

Intermittent pulses of steroids, such as prednisone, are a major component of maintenance therapy. Two publications evaluated adherence to prednisone during maintenance therapy for ALL [27][28]. Both were over 30 years old and used urine metabolites as a measure of nonadherence. Prevalence rates of nonadherence reported in these 2 articles were 33–42%. Smith et al. [28] also evaluated hemoglobin rise and weight gain as objective measures of adherence to prednisone, and did not demonstrate any significant relationship.

3. Behavioral Adherence

3.1. Medication Event Monitoring System (MEMS)

The MEMS cap is an objective, indirect measure of adherence to therapy. Microelectronic technology is used to record date and time of each pill bottle opening but does not provide information about ingestion of the medication [29]. Herein, 12 of 37 (32%) articles used MEMS as an assessment of adherence [21][29][30][31][32][33][34][35][36][37][38][39]. Adherence was calculated as ratio of number of days with MEMS cap opening to number of medications

prescribed as a percent. MEMS adherence over the course of 1 month ranged from 82–95%. Nonadherence was defined as MEMS adherence <90% or <95% based on an association with statistically significant increase in relapse when MEMS adherence rates fell below 90 or 95% [29]. All 12 publications assessed adherence to 6MP, with 9 reporting prevalence of nonadherence. In all except one [37], parents/patients were informed about the purpose of the MEMS and were instructed to take all doses of 6MP from the MEMS bottle. The prevalence of nonadherence for 6MP detected by MEMS was 21–58%. This was similar to the prevalence defined by low TGN and MMP metabolite cluster (21–41%) or TGN and MMP <95th percentile (53%).

Several studies sought to evaluate the relationship between MEMS behavioral adherence and pharmacological adherence measures [29][30][39]. Bhatia et al. [29][30] showed higher MEMS adherence correlating with increased TGN levels after accounting for *TPMT* activity and 6MP dose intensity. Rohan et al. [39] demonstrated that pharmacological nonadherence (defined by low TGN and MMP cluster) was associated with higher prevalence of behavioral nonadherence, defined by MEMS adherence <95%—63% compared to 48% seen in the low TGN and high MMP cluster. Furthermore, Bhatia et al. [31], in a third publication, showed a correlation between high intra-individual variability in MEMS adherence (coefficient of variation ≥85th percentile) and nonadherence, which was consistent with Davies et al. [11], demonstrating association of widely fluctuating TGN levels with nonadherence.

3.2. Tablet Counting

Tablet counting is an economical, objective, indirect measure of adherence which requires patients/families to return the number of pills prior to next prescription. Investigators can determine how many pills should be returned based on the month's prescription and any dose adjustments made during the month [40]. Like electronic monitoring, it does not provide information about ingestion of the medication. One study used tablet counting to evaluate adherence to daily 6MP and weekly MTX [41]. Nonadherence was defined as a tablet count difference greater than 3% from the prescribed number, implying an adherence of less than 97%. Prevalence of nonadherence during the baseline 3 months was 72%, higher than prevalence reported using other objective measures included here. Participants received remediation measures and, in the subsequent 3 months, prevalence of nonadherence decreased to 22%, but increased to 45% at 2 years. Unlike the studies with MEMS cap, there have been no studies to correlate pharmacological measures indicating increased medication exposure with tablet count adherence.

3.3. Prescription Review

Medication refill records can provide an objective, indirect measure of adherence of a large population of patients. Unlike electronic monitoring or tablet counting, refill records can minimize potential for patient or parent reactivity to being monitored [40]. However, refill records alone do not account for dose adjustments or provide information about medication ingestion. Only one publication used prescription review to assess adherence to daily 6MP and weekly oral MTX [42]. This research used a national claims database (Medical Outcomes Research for Effectiveness and Economics Registry) with all inpatient and outpatient claims and dispensed prescription medication claims. Adherence was measured as medication possession ratio (MPR), defined as sum number of

days of medication supplied/days in maintenance phase. Median MPR to 6MP was 85%, MTX was 81%. There was no defined parameter for nonadherence and no prevalence of nonadherence reported.

3.4. Medical Chart Review

Several articles used review of medical charts as a measure of nonadherence, using records of interruption or irregular dose administration [12][25][43]. This method detected a nonadherence prevalence of 30–31% for 6MP and 16% for MTX.

4. Subjective Adherence

4.1. Self-Report

Seventeen of 37 (46%) articles used self-reporting (participant survey or interview) as a subjective measure of adherence. Various methods were used, including structured or semi-structured interviews or questionnaires of patient and/or parents, specific validated questionnaires (Modified Morisky Adherence scale (MMAS) [3-, 4-, 8-item], Medication Adherence Report Scale, Chronic Disease Compliance Instrument, Visual Analogue Scale (VAS), Simplified Medication Adherence Questionnaire), and text survey. Self-report measures asked about missed medication doses in the past 1–2 weeks [44][45] or over the entire course of maintenance therapy [12][15][23][25][43]. The majority of the interviews and questionnaires were directed toward parents (n = 10); several included adolescents and young adults greater than 11 years old (n = 5). Self-reported medication adherence rate via surveys was between 93–97%. Definition of nonadherence was variable depending on method of self-reporting. Prevalence of nonadherence using these definitions were widely variable, between 0–73% for daily 6MP and 10–33% for weekly MTX. There was no consensus definition of nonadherence in self-reporting. Although each of the validated questionnaires had its own definition of nonadherence based on specific score cut offs, none of the publications used the same questionnaire, making comparisons between publications difficult. For example, Alsous et al. [10] used the Medication Adherence Report Scale (MARS) with score 0–5 (higher scores indicating better adherence) and a score of 4.5/5 (90%); they found prevalence of nonadherence of 5.8% based on parental response and 0% based on adolescent response. Even within the same study population, Heneghan et al. [46] found different rates of nonadherence using 2 different validated questionnaires—Modified Morisky Adherence Score 8-item (MMAS-8) and the Visual Analogue Scale. MMAS responses showed a prevalence of nonadherence of 43% based on parental responses and 73% based on adolescent responses, and VAS responses indicated a prevalence of nonadherence of 10% based on parental response and 12% based on adolescent response.

Survey or interview responses were also variable in their estimates of nonadherence depending on the definition of nonadherence and period of recall. When nonadherence was defined based on reports of not taking the medication, the prevalence was consistently low: 4–5% for MTX and 9% for 6MP, similar to the prevalence of 2–9% based on undetectable intracellular drug metabolite levels of 6MP or MTX. When surveys or interviews asked about recall of missed doses (at least 2) or non-exact medication administration over the entirety of maintenance, the prevalence of nonadherence increased, to 12–55% for 6MP and 10% for MTX. When the recall period was

shortened to the 1–2 weeks immediately prior, the prevalence of nonadherence, defined as missing 1 or more doses, was 25% for 6MP and 23% for MTX within 1 week, and 45% for 6MP within 2 weeks.

Four publications included both parent and adolescent responses to surveys. Adolescent responses resulted in 20–30% higher prevalence of nonadherence compared to parent responses [44][46][47]. Alsous et al. [10], on the other hand, detected a lower prevalence of nonadherence based on adolescent response compared to parental response (0% and 5.8% respectively), though both were significantly lower than prevalence reported in the other 2 publications. Heneghan et al. [46] analyzed 7 parent–adolescent dyads included in their sample and found no significant correlation between parent and adolescent responses on either self-report measure (VAS or MMAS-8), suggesting parents may not have provided accurate estimates of adolescent medication adherence.

4.2. Text Messaging

Psihogios et al. [38] performed a pilot study evaluating the use of daily text messages to assess 6MP adherence in adolescent and young adult patients. They found no significant correlation between text message response of adherence (97%) with MEMS cap opening (97%) over a 28-day period. However, the data did converge on a majority (>90%) of days and the authors concluded that daily text messages could be an acceptable and feasible method of assessing medication adherence.

4.3. Provider Survey

Three publications included surveys of physicians as a subjective measure of patients' medication adherence. Farberman et al. [47] and Mancini et al. [44] showed lower prevalence of nonadherence detected by physician survey responses compared to parent/adolescent responses (12–18% and 25–55%, respectively). However, Psihogios et al. [38] demonstrated similar adherence rates between participant text survey responses and physician survey responses (97% and 98%, respectively).

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