Loss of functional autonomy in medication management after start of therapy in older patients with haematological malignancies

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Summary. *Purpose:* Guidelines on older cancer patients recommend a comprehensive geriatric assessment, preferably including an item on medication management since cancer treatment further increases risks of polypharmacy. So far, little attention has been paid to non-adherence due to functional changes. We aimed to assess autonomy in drug self-administration after start-up of therapy in older patients with haematological malignancies. In case of inadequate compliance we tried to identify the causes. *Methods:* Longitudinal single centre cohort study in patients ≥70 years. Patients underwent a geriatric evaluation before and two months after start of therapy. Medication was registered both times. *Results:* Sixty-two patients, median age 77 years, were included. At baseline 49 patients (79%) took their long-term medication independently. Independent medication management was significantly higher in patients taking <5 medications (93.7% vs. 63.3%, p<0.005). After start of therapy, polypharmacy rates increased from 48.3% to 98.3% (n=61) while 55.6% of the initially independent patients became dependent for medication management. The median increase in the number of medications was significantly higher in dependent patients (6 vs. 4.5, p<0.05). Multiple daily doses (80%, n=50), varying doses (59.7%, n=37) and medication splitting (45.3%, n=27) further contributed to regimen complexity. Unlike results at baseline, no correlations were found between autonomy in medication management and medication regimen two months after therapy start-up. *Conclusion:* Haematological patients have to face a wide turnover of chemo drugs to treat malignancies. A considerable number of them require assistance in drug administration during their treatment: attention has to be paid to patient compliance, and improving it, highlighting the challenges of an ambulatory setting.

Key words: polypharmacy, haematological malignancy, comprehensive geriatric assessment, drug regimen complexity, older cancer patient, compliance with therapy

«Perdita di autonomia funzionale nella gestione della terapia domiciliare dopo l'inizio del trattamento in pazienti onco-ematologici di età avanzata»

Riassunto. *Obiettivo:* Il nostro obiettivo è quello di valutare l'autonomia nella gestione della terapia domiciliare in seguito all'inizio del trattamento nei pazienti onco-ematologici di età avanzata. In caso di diminuzione della suddetta, abbiamo cercato di individuare i fattori predisponenti. *Metodo:* Studio di coorte a singolo centro longitudinale in pazienti > di 70 anni. Tutti i pazienti sono stati sottoposti ad una valutazione geriatrica prima del trattamento e 2 mesi dopo. *Risultati:* 62 pazienti con età media di 77 anni sono stati reclutati; 49 pazienti (79%) hanno seguito la terapia assegnata autonomamente. La percentuale di pazienti che gestiva in modo autonomo la terapia era molto più alta nei pazienti con terapie composte da meno di 5 farmaci (93,7% vs. 63,3%, p<0,005). La politerapia è salita dal 48,3% fino al 98,3% (n=61) mentre il 55,6% dei pazienti ini-

zialmente indipendenti nella gestione della terapia domiciliare hanno perso la loro autonomia. L'incremento medio nel numero di farmaci si è rivelato più alto nei pazienti già dipendenti (6 vs. 4,5, p<0.05). Le dosi molteplici ripetute giornalmente (80%, n=50), le dosi variabili (59,7%, n=37) e la partizione del farmaco (45,3%, n=27) hanno contribuito ulteriormente alla complessità del regime terapeutico. Dopo due mesi di terapia non si è notata nessuna correlazione tra l'autonomia nella gestione della terapia domiciliare e le caratteristiche del regime farmaceutico stesso. *Conclusioni:* I pazienti hanno sperimentato un cambiamento nella terapia domiciliare mentre una quota considerevole è diventata dipendente nella gestione della stessa. Maggior attenzione andrà posta al rilevamento e alla risoluzione di tali problematiche, prendendo in considerazione anche la possibilità di instaurare una terapia ambulatoriale.

Parole chiave: politerapia, neoplasie ematologiche, valutazione geriatrica completa, complessità dello schema terapeutico, pazienti oncologici anziani

1. Introduction

The incidence rates of haematological malignancies increase steadily with age. Treating older patients suffering from aggressive haematological malignancies is becoming a challenging task for all caregivers involved, since the heterogeneity of the aging process is characterised by marked variability in the rate of functional loss, both between and within individuals (1, 2). However, chronological age does not reflect these individual differences and therefore is not a good predictor of remaining functional reserves or life expectancy. Guidelines on older cancer patients, such as those from the National Comprehensive Cancer Network (NCCN) or the International Society of Geriatric Oncology (SIOG), recommend the use of a Comprehensive Geriatric Assessment (CGA) as a multidimensional, interdisciplinary diagnostic process focusing on determining a frail older person's physical, psychological and functional capabilities (3-5). Although no gold standard exists, there is consensus that the CGA should include functional, cognitive, emotional and psychosocial status as well as the aspects of nutrition, mobility and polypharmacy, in addition to comorbidity assessment (6).

Polypharmacy schedules involving five or more drugs, with increased drug regimen complexity and risk of adverse drug reactions (ADRs), drug-drug interactions (DDI), inappropriate self-medication and poor drug adherence are an area of concern, especially in older patients. In the older cancer cohort, chemotherapy and supportive drugs to prevent side-effects or treat the symptoms additionally increase the risks and complications of polypharmacy. Guidelines recommend reviewing the number and the type of medications in all patients and, in case of more than three medications, looking for duplications, interactions, and non-adherence (6). Studies on the optimization of geriatric pharmacotherapy focus most commonly on pharmacological outcomes and prognosis, ADRs and potentially inappropriate medication. However, little attention has so far been paid to (unintentional) non-adherence due to functional problems or changes, despite the well-known fact that older patients experience a gradual decline in their cognitive and functional abilities which are required for medication management.

Although a CGA, as a multidimensional diagnostic process, generally includes an evaluation of functional, cognitive, emotional and psychosocial status as well as the aspects of nutrition, mobility and polypharmacy, the assessment tools included may differ widely. Nevertheless, most CGAs currently used in studies do not include an item on medication management, except for one item in the Lawton Instrumental Activities of Daily Living Scale (IADL) (7). Apart from "taking medication as prescribed", seven more independent living skills are assessed. For each of these skills one can identify the overall social and autonomous patient function at time 0 and whether an improvement or deterioration follows upon it.

In our study population, based on IADL assessment during treatment, we aimed to assess autonomy in medication management after the start of therapy in older patients with a haematological malignancy. Additionally, in case of deterioration, we aimed to search for predetermining factors.

2. Materials and methods

2.1 Patients

This was a longitudinal single centre cohort study. All patients aged 70 years or older with a new diagnosis of Acute Myeloid Leukaemia (AML), intermediate or high grade Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM) or high grade Non Hodgkin Lymphoma (NHL) who were referred to the haematology department of a tertiary hospital between June 2011 and January 2013 were asked to participate in the current study. All participants provided written consent. The study was approved by the local Ethics Committee.

2.2 Geriatric evaluation

Before chemotherapy administration all patients underwent Comprehensive Geriatric Assessment (CGA) by a member of the geriatric team. Since no gold standard exists, our CGA consisted of a set of six questionnaires, i.e. Activities of Daily Living (ADL) (8), Instrumental Activities of Daily Living (IADL) (7), 4-item Geriatric Depression Scale (GDS-4) (9), Mini Mental State Examination (MMSE) (10), Mini Nutritional Assessment – Short Form (MNA-SF) (11), and any falls in the previous year. Comorbidity was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). In addition, patients were asked some questions on social and financial items. This geriatric evaluation was repeated two to four months later, depending on the treatment schedule.

The Lawton IADL Scale, based on self-reporting, is validated in older people to assess independent living skills at a given moment as well as over a certain period of time. There are 8 domains of function measured: ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Each item is rated dichotomously (0=less able, 1=more able) according to the highest level of functioning in that category. Specifically for medication intake patients score 1 point only when they are able to manage their medication completely independently. If someone else is preparing the medi-

cation in advance, a patient scors 0 points, even if he/she is taking his/her pills autonomously throughout the day.

2.3 Medication review

Current medication was registered on study enrolment and two months later. Medication lists, as written down in the letter to the treating general practitioner, were reviewed shortly after the start of therapy. Polypharmacy was taken to mean a 5-medication schedule. In the initial design of the study (and thus before the results of IADL were available) eye-drops, mouth rinses and topical creams were not taken into account as these products were unlikely to produce a systemic effect. Neither did we take into account those medications a patient need only take if necessary, (e.g. pain killers only used if pain is present), as it was not known whether or not the patient was taking such medication.

2.4 Statistical methods

Descriptive analyses were performed to describe patients' characteristics and geriatric evaluation results. Continuous variables were expressed as a median and range. Countable variables were presented as an absolute number (n) and percentage (%) of the study population. To assess differences between categories, the Pearson chi-square test was used. Univariate logistic regression analysis was used to identify medication regimen characteristics associated with (in)dependent medication management. All analyses were performed in Medcalc® Version 12.7.0.0 (Medcalc Software bvba).

3. Results

Sixty two patients were included in the study. Baseline characteristics are presented in Table 1. The median age was 77 years (range 70-91). The results of the geriatric evaluation as well as changes in IADL over time are presented in Table 2. At baseline 49 patients (79%) took their chronic medication without any assistance. Independent medication management was

Table 1. Baseline characteristics of the patients (N=62)

Sex, n (%)	
Male	30 (48.4)
Female	32 (51.6)
Age (years), n (%)	
<75	19 (30.6)
75-80	26 (41.9)
>80	17 (27.4)
Diagnosis, n (%)	
Acute Myeloid Leukaemia	16 (25.8)
High Grade Lymphoma	24 (38.7)
Myelodysplastic Syndrome	12 (19.4)
Multiple Myeloma	7 (11.3)
Number of comorbidities, median (range)	
Grade 1-2	4 (0-9)
Grade 3-4*	1 (0-4)

*current haematological diagnosis not included

Table 2. Results of the geriatric evaluation (N=62)

Living status, n (%)	
Alone	24 (38.7)
Living with spouse	33 (53.2)
Living with family member (other than spouse)	4 (6.5)
Long term care facility	1 (1.6)
"Do you expect financial problems because of your disease?", n (%)	
Yes	4 (6.5)
No	58 (93.5)
Patients with MMSE * <24, n (%)	3 (4.8)
Number of patients (N=46) with decline from baseline in individual IADL-items, n (%)	
Ability to use telephone	1 (2.2)
Shopping	13 (43.3)
Food preparation	9 (33.3)
Housekeeping	12 (33.3)
Laundry	13 (46.4)
Mode of transportation	12 (41.4)
Responsibility for own medications	20 (55.6)
Ability to handle finances	2 (4.4)

* Mini Mental State Examination

significantly higher in the group of patients taking less than 5 medications (93.8% vs. 63.3%, p < 0.005). Two months after the start of therapy 8 patients died and 6 were lost to follow up. Of the formerly independent patients, 55.6% (20 of the remaining 36) needed assistance with their medication.

Table 3. Medication and medication regimen characteristics (N=62)

Patients with at least 1 demanding dosage form, n (%)	25 (40.3)
Tablet splitting, n (%)	27 (43.5)
≥1 drug with multiple doses per day, n (%)	50 (80.6)
≥1 drug with different dosages depending on time of week, n (%)	37 (59.7)
≥12 drug administrations per day, n (%)	28 (45.1)
≥3 drugs with different dosing intervals, n (%)	18 (29.0)
N° of drug prescriptions, n (%) :	
Cardiovascular agents	151 (28.6)
Supportive agents	152 (28.8)

Polypharmacy was being administered in 48.4% of patients (n =30) at the time of diagnosis and increased to 98.3% (n=61) during follow up. Likewise, the intake increased from a median of 4 (0-10) medications to a median of 9 (4-16) medications and 11 (4-22) pills a day. In patients dependent for medication management at baseline, the median increase in the number of medications was significantly higher than in their independent counterparts (6 vs. 4.5, p<0.05). The medication regimen characteristics are presented in Table 3. Unlike results at baseline, no correlations were found between autonomy in medication management and medication regimen characteristics two months after the start of therapy.

4. Discussion

According to the guidelines, every older patient with cancer should undergo a geriatric assessment (4, 5). In our study population, the assessment was repeated two months after the start of therapy and compared with baseline evaluation. Two main aims of our study were to assess autonomy in medication management after the start of therapy and, in cases of deterioration, to search for predetermining factors.

At baseline 21% of patients needed assistance with medication intake, which is comparable to what we found in the literature (12, 13). Independent medication management was significantly higher in the group of patients taking less than 5 medications

(p<0.005). Two months after the start of therapy, rates of polypharmacy, and hence drug regimen complexity, increased from 48% to 98% and from a median of 4 to a median of 9 prescription drugs, while more than half of the remaining and initially independent patients became dependent for medication intake. Moreover, in patients dependent for medication management at baseline, the median increase in the number of medications was significantly higher (p<0.05).

Drug regimen complexity has generally been defined as the number of medications and daily administrations of distinct drugs (14-16). This definition does not take into account other regimen characteristics that might contribute to drug regimen complexity: tablet splitting (13, 16-18), the route of drug administration (17, 19, 20), different doses throughout the day or week (17, 19, 20), drugs with multiple doses per day (15) or with different dosing intervals (14, 20), all of which were present in a considerable percentage of medication lists. Drug regimen complexity is related to patient non-adherence but also to medication errors, adverse drug events and therapeutic failure (14, 20).

With regard to the second aim, in contrast with the results at baseline, we could no longer find a correlation between polypharmacy and autonomy in medication management, neither could we find a correlation between regimen complexity and (in)dependence in medication intake.

The most plausible explanation for this lack of statistical significance is the relatively small sample size. Furthermore the binary coding of IADL-items does not allow one to differentiate between degrees of dependence: patients already dependent for medication, albeit just needing pills to be prepared once a week by a caregiver using a dose administration aid, will keep the same score even if, after two months, the patient has moved to a nursing home where his medication is brought to him at set times.

As the IADL-item on "responsibility for own medications" purely addresses the practical aspects of medication management and provides no information as to the cause of the incapacity, plausible explanations other than regimen complexity were considered. General weakness, as a result of their illness and treatment, might be one. This is, however, doubtful if we look at other IADL-domains like housekeeping and food preparation, both physically demanding, where the percentage of patients with a decline proves less prominent. Cognitive decline is also unlikely as MMSE-scores remained stable over time and were, except for 3 patients, within the normal range. We therefore believe that the loss of autonomy for medication management is largely related to regimen complexity.

For patients living together medication management is often taken over by the spouse. Spouses, in most cases, are as old as their partner and the same evaluation might apply to the spouse as well. However, patients without a spouse might be left on their own. Clinicians often fail to predict correctly a patient's cognitive and/or functional capacity to manage medication (21) while patients might not report potential problems unless they are specifically asked, for example in the course of a geriatric evaluation. No studies are available addressing the issue of self-medication becoming unsafe and when to switch medication management to an informal or formal caregiver (21).

The findings of this study might make health care professionals in charge of older patients with haematological malignancies more aware of the impact of polypharmacy, frequent regimen changes and drug regimen complexity during treatment, and draw their attention to some unmet needs. Multidisciplinary teams including pharmacists and well-trained nurses or nurse specialists are already involved in medication reconciliation and patient education in order to improve medication adherence (21, 22). However, in older patients with cancer, at least during treatment, increased emphasis should be placed on direct observation of medication handling for both patient and spouse, preferentially using a patient's own medication (23, 24). In an era where health care systems are asked to establish quality indicators with an emphasis on appropriate medication use, our present findings call for development of a specific "self-administration of medications program" for older ambulatory cancer patients based on information, education and medication preparation under nursing supervision.

Our study had several limitations. First, the study was a single-centre study with a small sample size. Second, we did not take into account eye-drops, mouthwash and topical creams, or prescriptions for "as needed" medication. Although non-oral medications

are probably less related to adverse drug reactions, they certainly contribute to the complexity of medication regimens. Inclusion of these medications would additionally have emphasized the magnitude of the problem. Third, we have no information as to the cause of the incapacity, but whatever the reason might be, the need for individual appraisal of medication management remains. Finally, the appropriateness and quality of prescribing was not assessed.

In conclusion, haematological patients are subject to extensive changes in their medication regimen at the start of therapy. A considerable number of these patients show loss of independence for medication management. Future research, based on a larger study population, and future care pathways should focus on detection and remediation, taking particularly into account the challenges of an ambulatory setting.

Acknowledgement

Conflict of interest

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