ORIGINAL RESEARCH

Medication Reconciliation Associated with Comprehensive Geriatric Assessment in Older Patients with Cancer: ChimioAge Study

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Background: Polymorbidity induces polypharmacy in older patients may lead to potential drug–drug interactions (DDI) which can modify the tolerance and safety of oncological treatments and alter the intended therapeutic effect. The objective of our study was to describe the decision-making process for oncological treatment and related outcomes, in a population of older adults undergoing a comprehensive geriatric assessment (CGA) associated to a comprehensive medication reconciliation (CMR) prior to initiating oncological treatment.

Methods: ChimioAge is a prospective observational study conducted between 01/2017 and 07/2018 at Marseille University Hospital and approved by the French National Ethics Committee. It comprised all consecutive patients aged 70 years and over who were referred for a CGA as part of CMR, before initiating systemic treatment.

Results: One hundred and seventy-one cancer patients were included. Mean age was 79.2 years, over half had metastatic cancers, 75% had an ECOG performance status zero or one, and two-thirds were independent in daily activities. Two-thirds of the patients had polypharmacy and the CMR identified potential DDI with systemic treatment in 43.3% of patients. Following the CGA, the CMR and the hospital oncologists decision, 30% of the patients received adapted systemic treatment with reduced doses at initiation. They presented fewer toxicities – irrespective of grade and type – than patients who received standard treatment (p<0.001) and had comparable overall survival (Log rank p=0.21).

Conclusion: This is one of the first studies to highlight the value in conducting CMR and a CGA simultaneously before initiating systemic treatment in older patients with cancer. These two evaluations could give oncologists decisive information to personalize cancer treatment of older patients and optimize treatment dose to offer the best efficacy and minimize toxicity.

Keywords: aged, antineoplastic protocols, geriatric assessment, medication reconciliation, treatment failure

Introduction

Aging and cancer are closely linked, as aging leads to complex cellular, molecular, and physiological changes associated with accumulation of genetic changes, which can result in the development of cancer.[1] Cancer affects nearly 50% of people over 65 years worldwide according to Globocan data,[2–4] in the USA, and nearly 60% of people aged 65 years and over in Europe.[5,6] Although older patients are the most affected by cancer, they are still under-represented in clinical trials, especially in an oncological setting.[7] However, it is known that drug pharmacokinetics change

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substantially with aging and vary according to the patient's history. For example, malnutrition is common in older patients with cancer, and results in a decrease in albumin which modifies the pharmacokinetics of drugs that bind strongly to plasma proteins, and hence their efficacy and toxicity.[8] Clinical features of older people are heterogeneous, with frequent comorbidities and associated polypharmacy (5 or more drugs per day). When managing older adults with cancer, potential drug interactions (DDI) between these drugs and the chemotherapy delivered should be considered, as these interactions may modify the tolerance of the cancer treatment and alter the intended therapeutic effect.[9,10] Recent studies have shown that major DDI are very prevalent in older adults with cancer and are a risk factor for early and unplanned hospitalizations.[11,12] In this particular context, the International Society of Geriatric Oncology (SIOG) recently recommended establishing close cooperation with pharmacists as part of the Comprehensive Geriatric Assessment (CGA)[13] in order to review prescriptions of older patients with cancer and avoid adverse side effects of treatment.[14] This pharmaceutical intervention is called comprehensive medication reconciliation (CMR)[15,16] and the clinical pharmacist is fully integrated into the multidisciplinary team.[17] The ChimioAge study was implemented in our hospital in January 2017, to evaluate the impact of the association CGA-CMR on the oncological management of older cancer patients. The aims of the following analysis were to describe the potential impact of the geriatric and pharmaceutical advice provided on dose reduction of oncological treatment, early discontinuation and toxicities.

Methods
Study Design
The ChimioAge study is a prospective observational study.

Study Duration, Site and Sample Size
Between January 2017 and July 2018, 171 patients were enrolled at Marseille University Hospital (AP-HM).

Participants
All consecutive patients, aged 70 years or over referred for geriatric advice before initiation of systemic treatment.

Inclusion Criteria
Patients included were 70 years and older, who agreed to participate in the ChimioAge Study, underwent both CGA

and CMR, and received systemic treatment. Systemic treatment included cytotoxic therapy and/or targeted therapy and/or immunotherapy.

Exclusion Criteria
Patients under guardianship or curatorship who were currently enrolled in another clinical study were excluded from the study.

Ethical Approval
In accordance with the declaration of Helsinki, the study protocol was submitted and approved by an Ethics Committee (CPP Ouest IV – Nantes registered 61/18_3) and registered in ClinicalTrials.gov (NCT03960593).

Data Collection and Measurements at Baseline
A multidisciplinary team comprising a geriatrician, pharmacists, nutritionists, and nurses collected the data. A hospital pharmacist first conducted a systematic review of all the medications each patient was taking in order to detect drugs that can cause interactions with oncologic systemic treatment. Drugs informations were collected from the patient and/or caregiver, the most recent medical prescription, and the patient's medical record. The CMR included indications and doses of the prescribed drugs, as well as an evaluation of self-administration of non-prescribed medication and consumption of medicinal products (phytotherapy, herbs and spices).

All the medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification, as recommended by the World Health Organization. The pharmaceutical analysis was performed using Vidal Hoptimal® and Drugs.com® and DDI was performed using STOPP criteria.[18] Polypharmacy was defined as the simultaneous use of a minimum of five prescribed medications.

A geriatrician collected the different components of the CGA: G8 screening tool (impaired ≤ 14/17),[19] vulnerability score (ECOG-PS) (impaired ≥ 2),[20] Activities of Daily Living (ADL) (impaired < 6/6),[21] Instrumental Activities of Daily Living (IADL) scales (impaired < 4/4).[22] Cognitive disorders and depressive mood were respectively assessed by the Mini Mental State Examination scale (MMSE) (impaired MMSE < 24),[23] and the short Geriatric Depression scale (impaired GDS≤1/4).[24] Body Mass Index (BMI), albumin levels,

and Mini Nutritional Assessment scale (MNA)[25] were used to determine the nutritional status as defined by the French Department of Health (malnutrition = BMI < 21 and/or albumin levels < 35 g/l and/or MNA < 17)). Patients' mobility was assessed using gait speed (impaired < 0.8m/s),[26] Timed Up and Go Test (impaired TUG > 20s),[27] One Leg Balance test (impaired OLBT < 5s),[28] fall history over the past three months, and handgrip strength (impaired < 27 kg for men; < 16 kg for women)[29]). Patients were asked about their demographic characteristics and lifestyle (age, living place, and presence of a caregiver). Severe comorbidities were identified using the geriatric Cumulative Illness Rating Scale (CIRS-G).[30] Primary medical information was obtained from the medical records: cancer site and stage, detailed treatment, and biological data. Renal function was assessed using the Cockcroft creatinine clearance (renal failure if clearance < 30 μmol/L), anemia was defined by a level of hemoglobin ≤ 11.5 g/dl, thrombopenia was defined by a platelets level <150 G/l and lymphopenia by a lymphocytes level <1.26 G/l.

At the end of the CGA, the geriatrician adapted the patient's treatment according to the CMR results and gave recommendations to the patient to avoid self-medication, herbals and spice that could interfere with oncological treatment.

Follow-Up Data and Measurements

Data on cancer progression and treatment were obtained from medical records: number of systemic treatment cycles, toxicities, oncologic treatment adaptation (ie, dose reduction) and premature discontinuation, as well as causes for treatment adaptation and discontinuation.

A total number of frailties (from 0 to 6) was computed by giving 1 point to each of the following frailties: CIRS-G severe comorbidities, malnutrition, polypharmacy, cognitive disorders, impaired mobility and/or handgrip strength decrease, impaired autonomy for the instrumental activities of daily living. These particular frailties were selected by the geriatrician as the main domains used to determine systemic treatment dose adaptation. The hospital pharmacist conducted follow-up calls with the patients at 30, 60, and 90 days after enrollment to collect information about unplanned hospitalizations and overall survival (OS) (collected up to January 2019).

Premature systemic treatment discontinuation was defined as treatment discontinuation before the fourth systemic treatment cycle related to cancer progression, toxicity, other reasons or death. OS was defined as the time between date of CGA and date of death or last known follow-up.

Statistical Analysis

A descriptive analysis was performed to describe the main demographic, oncological, geriatric, and treatment characteristics of our population using headcounts and percentages for discrete data as well as mean values plus or minus the standard error and the interval between the minimum and maximum values for continuous data. Comparative analysis were performed to compare patients according to initial doses of systemic therapy (reduced doses vs standard doses), premature systemic treatment discontinuation (yes vs no), and presence of toxicities grade 3–5 (yes vs no). The Chi-squared test was used to analyze discrete data whereas Student's t-test was used to analyze continuous variables. A Kaplan-Meier analysis was used to compare the overall survival rates in two groups of patients: those who received reduced doses at systemic therapy initiation, and those who received standard doses. All the statistical analyses were performed using SPSS software (version 17.0).

Results
Descriptive Analysis

A total of 171 older patients with cancer who received systemic treatment after a CGA and a CMR were included in the survey.

Socio-demographic and baseline medical characteristics of the study population are detailed in Table 1. The mean age was 79.2 years (SD 5.2). Only 10 patients had hematologic malignancies, and nearly one-third had lung cancer. A majority of patients with solid tumors had metastatic cancer (53.2%). Table 2 displays the results of the CGA. Most patients had good performance status (74.9% patients with ECOG-PS score 0 or 1) and 66.1% of patients were independent in daily activities. The mean number of frailties per patient was 2.3 ±1.4 (from 0 to 6).

Nearly two-thirds of the patients were prescribed more than five drugs (64.9%), and the medication reconciliation identified potential interactions with oncologic treatment in 74 patients (43.3%). Personal drugs were adapted in accordance with General Practitioners (GPs) to take into account the potential DDI.

Table 1 Socio-Demographic and Medical Characteristics at Baseline According to Systemic Therapy (Standard Doses vs Reduced Doses at Initiation) (n=171)

	Total (n=171)		Treatment Initially Adapted				P value
			Yes (n=51)		No (n=120)		
	n	(%)	n	(%)	n	(%)	
Gender							0.67
Men	98	(57.3)	28	(54.9)	70	(58.3)	
Women	73	(42.7)	23	(45.1)	50	(41.7)	
Age (years)							0.11
70–74	37	(21.6)	8	(15.7)	29	(24.2)	
75–79	54	(31.6)	16	(31.4)	38	(31.7)	
80–84	47	(27.5)	20	(39.2)	27	(22.5)	
85 and more	33	(19.3)	7	(13.7)	26	(21.6)	
Living alone at home	31	(18.1)	9	(17.6)	22	(18.3)	0.91
Caregiver*	110	(64.7)	35	(68.6)	75	(63.0)	0.48
Cancer localisation							0.19
Lung	53	(31.0)	12	(23.5)	41	(34.2)	
Breast or Gynecologic	32	(18.7)	16	(31.4)	16	(13.3)	
Gastrointestinal	27	(15.8)	7	(13.7)	20	(16.7)	
Head and neck	19	(11.1)	7	(13.7)	12	(10.0)	
Prostatic or Urologic	20	(11.7)	4	(7.8)	16	(13.3)	
Skin	7	(4.1)	1	(2.0)	6	(5.0)	
Hematologic malignancies	10	(5.8)	3	(5.9)	7	(5.8)	
Other	3	(1.8)	1	(2.0)	2	(1.7)	
Metastasis	91	(53.2)	27	(52.9)	64	(53.3)	0.96
Medical history in the past 3 months							
Fall History	32	(18.7)	11	(21.6)	21	(17.5)	0.53
Emergency admission	27	(15.8)	7	(13.7)	20	(16.7)	0.63
Hospitalization**	71	(41.8)	21	(41.2)	50	(42.0)	0.91

Notes: *1 missing value. ** 2 missing value

All patients received cancer systemic treatment; the majority received chemotherapy (74.1%) (Table 3).

Dose Reduction at Treatment Initiation

A total of 51 patients (29.8%) received reduced doses of systemic treatment at initiation. In the majority of cases (75%), reduction of doses at treatment initiation was made according to the recommendations of both CGA and CMR. Decision of treatment reduction was more often observed in patients dependent on activities for daily living (Table 2).

Only 33.7% of the whole sample received full standard treatment, 29.8% received adapted treatment and 35% had further dose reduction during the treatment course. Toxicities were much more frequent in patients who benefited from standard treatment than patients whose treatment was initially adapted (54.2% vs 9.8% - p<0.001) (Table 3).

Figure 1 depicts the 2-year OS by treatment modality (initially adapted treatment vs standard treatment). Median OS was higher in patients who received standard doses of systemic treatment at initiation, but the difference did not reach statistical significance (Log rank p=0.21).

Premature Discontinuation of Systemic Treatment

Systemic treatment was prematurely discontinued in 38 patients (22.5%). Causes for discontinuation were disease progression (n=15), toxicity (n=13), other reasons (n=6), and death (n=4) (Table 3). A univariate comparative analysis showed that early oncological treatment discontinuation was more often observed in men, aged 80 to 84 years,

Table 2 Geriatric and Pharmacological Characteristics at Baseline According to Systemic Therapy (Standard Doses vs Reduced Doses at Initiation) (n=171)

Variables	Total (n=171)		Treatment Initially Adapted				P value
			Yes (n=51)		No (n=120)		
	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	
ECOG-PS >2	43	(25.1)	13	(25.5)	30	(25.0)	0.94
G8 ≤14	149	(87.1)	44	(86.3)	105	(87.5)	0.83
ADL<6	58	(33.9)	23	(45.1)	35	(29.2)	0.04
IADL* <4	90	(52.9)	28	(54.9)	62	(52.1)	0.73
Urinary incontinence	18	(10.5)	10	(19.6)	8	(6.7)	0.01
MMSE <24 (n=157)	29	(18.5)	12	(26.1)	17	(15.3)	0.11
GDS ≥1 *	37	(21.8)	15	(30.0)	22	(18.3)	0.09
Nutritional status							
Malnutrition #	59	(34.5)	19	(37.3)	40	(33.3)	0.62
Mobility							
TUG > 20s (n=168)	65	(38.7)	23	(45.1)	42	(35.9)	0.26
OLBT< 5s (n=153)	99	(64.7)	23	(56.1)	76	(67.9)	0.17
Gait speed < 0.8m/s (n=155)	42	(27.1)	15	(34.9)	27	(24.1)	0.17
Impaired handgrip strength##	66	(38.6)	20	(39.2)	46	(38.3)	0.91
Number of comorbidities **	3.56±2.4	[0–13]	3.1±2.0	[0–8]	3.7±2.6	[0–13]	0.13
Severe comorbidities	73	(42.7)	26	(51.0)	47	(39.2)	0.15
Number of frailties	2.29±1.4	[0–6]	2.6±1.6	[0–6]	2.2±1.4	[0–5]	0.06
Biological status							
Renal failure (n=165)	7	(4.2)	2	(4.0)	5	(4.3)	0.91
Thrombopenia (n=166)	21	(12.8)	4	(7.8)	17	(14.8)	0.21
Lymphopenia (n=165)	29	(17.6)	6	(11.8)	23	(20.2)	0.19
Anemia (n=167)	64	(38.3)	20	(39.2)	44	(37.9)	0.87
Polymedication (≥5 drugs)	111	(64.9)	33	(64.7)	78	(65.0)	0.97
Identification of potential drug interaction *	74	(43.3)	24	(47.0)	50	(41.6)	0.54

Notes: Anemia: Hb <11.5 G/dL Thrombopenia (<150 G/L) Lymphopenia: (<1.26G/L). #Malnutrition: BMI<21; Albumin <35g/L; MNA<17. ##Impaired Handgrip strength: < 27 kg for men and < 16 kg for women. *1 missing value - **2 missing values.
Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; TUG, Timed Up and Go Test; OLBT, One-Leg Balance Test.

and in patients suffering from lung or gastrointestinal cancer. No geriatric characteristic was associated with premature systemic treatment discontinuation (Table 4).

Toxicities

A total of 70 patients (40.9%) suffered from toxicities, and 24 of these from severe toxicities (10/24 hematological toxicities, 5/24 digestive toxicities and 9/24 other toxicities (including neuropathy, skin toxicities and asthenia)). Grade 3–5 toxicities were mostly observed in patient who benefited from standard treatment and were the major cause of premature treatment discontinuation (Tables 3 and 4). The occurrence of toxicities was independent of patients' geriatric characteristics (Table 5).

Discussion

This is one of the first studies to show the potential benefits of a close collaboration between oncologists, geriatrician and pharmacists for older patients with cancer before initiation of systemic treatment. Our results showed the high frequency of polypharmacy (65%) and potential DDI (43%) among older cancer patients, and confirmed the major utility of using CGA to assess frailties and to detect potential DDI and oncological treatment interactions in older adults before the initiation of cancer management. In our study, the dose reduction at oncological treatment initiation after CGA and CMR association reduced grade 3–5 toxicities in older adults treated for cancer and had no significant impact on their overall survival.

Table 3 Clinical Follow-Up Data 3 Months After Treatment Initiation According to Systemic Therapy (Standard Doses vs Reduced Doses at Initiation) (n=171)

Variables	Total (n=171)		Treatment Initially Adapted				P value
			Yes (n=51)		No (n=120)		
	N	(%)	N	(%)	N	(%)	
Systemic treatment (n=168)							0.02
Chemotherapy	117	(74.1)	80	(76.9)	37	(68.5)	
Targeted therapy	19	(12.0)	13	(12.5)	6	(11.1)	
Immunotherapy	8	(5.1)	1	(1.0)	7	(13.0)	
Chemo and targeted therapy	12	(7.6)	8	(5.1)	4	(2.5)	
Chemo and immunotherapy	2	(1.3)	2	(1.3)	–	–	
Reduction of treatment doses (n=166)							<0.001
None	56	(33.7)	–	–	56	(48.3)	
<25%	58	(34.9)	27	(54.0)	31	(26.7)	
25–49%	31	(18.7)	14	(28.0)	17	(14.7)	
>50%	21	(12.6)	9	(18.0)	12	(10.3)	
Type of treatment							
Mono-therapy	64	(37.4)	17	(33.3)	47	(39.2)	0.47
Bi-Therapy	89	(52.1)	25	(49.1)	64	(53.3)	0.60
Tri or quadri therapy	18	(10.5)	9	(17.6)	9	(7.5)	0.05
Unplanned hospitalization (n=135)	51	(37.8)	17	(40.5)	34	(36.6)	0.66
Premature TRT discontinuation (n=169)	38	(22.5)	13	(25.5)	25	(21.2)	0.54
Cancer progression	15	(39.5)	6	(16.2)	9	(36.0)	
Toxicity	13	(34.2)	2	(15.4)	11	(44.0)	
Other reasons	6	(15.8)	3	(23.1)	3	(12.0)	
Death	4	(10.5)	2	(15.4)	2	(8.0)	
Toxicities							
None	101	(59.1)	46	(90.2)	55	(45.8)	<0.001
Grade 1–2	46	(26.9)	3	(5.9)	43	(35.9)	
Grade 3–5	24	(14.0)	2	(3.9)	22	(18.3)	

In our survey, systemic treatment was initially adapted for 29.8% of the patients. In a review by Hamaker et al,[31] after CGA, oncological treatment was changed by oncologists for a median of 28% of patients (range 8–54%), and these modifications resulted in the decision to adopt a less intensive treatment in the majority of cases. Moreover, further dose reduction during the course of systemic treatment concerned 35% of our patients, in accordance with literature. Kotzerke et al, showed that the dose reduction rate during systemic treatment reached 38% in a cohort of 104 older patients treated with chemotherapy,[32] and 31% in a sample population of 494 patients treated with chemotherapy in Aaldriks et al.[33] Chemotherapy dose reduction is controversial because it may lead to a reduction in relative dose intensity and compromise treatment efficacy. Some studies have shown that chemotherapy toxicity in older

adults was probably counterbalanced by the positive effect of oncological standard systemic treatment.[34] However, as already reported in the literature,[31] we found that initial treatment reduction had no negative impact on the overall survival of older patients with cancer.

In practice, many reasons may lead oncologists to modify chemotherapy doses in older adults. Nevertheless, in the literature, the respective impact of CGA and clinical judgement in these modifications is unclear. CGA domains or tumor type have never been proven to be associated with dose reduction, particularly at treatment initiation.[35–39] In our work, two thirds of initial dose reductions were secondary to CGA and CMR advice, and we found that two geriatric factors were associated with initial dose reduction: autonomy impairment in the activities of daily living and urinary incontinence. This confirms findings of
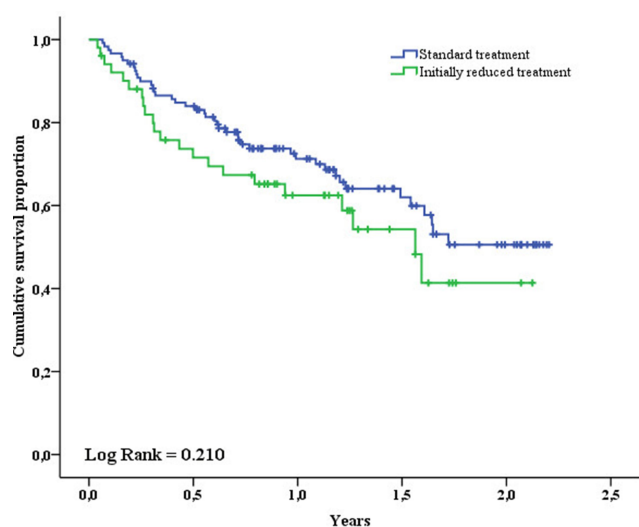
Figure 1 Overall survival standard treatment versus adapted treatment.

a previous study, where we showed that functional impairment was decisive for cancer management in older patients.[40] Even when the geriatric characteristics of the patients (assessed by the CGA) do not contra-indicate systemic treatment for their cancer, a minor loss of autonomy or the presence of minor frailties may lead the geriatrician to recommend an adaptation of cancer treatment.

In our study, the use of a systemic treatment based on tri or quadri-therapy was another factor associated with initial dose reduction in older adults treated for cancer. Polychemotherapy and systemic therapy associations are known to be associated with toxicity.[39,41,42] In particular polychemotherapy carries a higher risk of toxicity than monotherapy,[39,41,43] which may lead the oncologists to decrease initial polychemotherapy doses. Two scores have recently been developed to predict severe chemotherapy toxicity in older patients: the CARG score (Cancer and Aging Research Group score)[41] and the CRASH score (Chemotherapy Risk Assessment Scale for High-Age Patients).[42] They are not yet used in routine practice by oncologists and they could be recommended to guide chemotherapy management[32] as part of multidisciplinary care of older patients.

Toxicity rates found in our study were lower than those previously described, irrespective of toxicity grade. Fourteen percent of the sample population presented grade 3–5 toxicities, although around 57–64% severe grade of toxicities are usually reported in the literature.[32,44,45] The percentage of severe toxicities was even lower in patients with initially reduced treatment (4%) than in patients with standard treatment (18%). The difference observed in frequency of grade 3–5 toxicity in our study compared to

others may also be imputable to the multidisciplinary management set up after CGA and CMR. CMR recommendations, associated with geriatricians' interventions have been effective at identifying and managing geriatric frailties and medication-related risks,[46,47] and at decreasing severe chemotherapy toxicity.[48] This decrease of toxicity rate, including grade 1–2 toxicities, is important to preserve functional status and quality of life of older patients. Indeed, decreasing the frequency of lower-grade toxicities has been shown to be as important as decreasing the frequency of higher-grade toxicities for optimizing quality of life domains.[49] Consequently, oncologists may choose to modify or stop systemic treatment to protect older patients from lower-grade toxicities and preserve their quality of life.[44] In this regard, appropriate adaptation of the treatment is an important step to decrease both lower- and higher-grade toxicities as shown in our data (Table 3). Management of high-grade toxicities encompass hospital care, as recommended by ASCO and ESMO, and is responsible for unplanned hospitalizations. By decreasing the incidence of severe toxicities, CMR associated with CGA could also help to reduce healthcare costs.[50]

In the literature, chemotherapy toxicity was associated with age,[51] geriatric factors as cognitive troubles[39] or comorbid conditions.[45] Geriatric factors were not associated with systemic therapy toxicity in our work, showing that adequate geriatric management may reduce or even eliminate frailties linked toxicities.

The systemic treatment discontinuation rate of 22.5% found in our study is consistent with literature findings that report treatment discontinuation rates between 24 and 40%.[32,52] According to our results, toxicity was the second most common cause of systemic treatment discontinuation after disease progression, concurring with literature[32,33,52] and geriatric factors were not associated to chemotherapy discontinuation, controversially with other studies.[33,52–54] This important finding confirms the benefits of performing a CGA before deciding on oncological treatment in older patients, as recommended at international level.[13] A majority of the patients of our study sample had a G8 ≤ 14 but few had impaired functional status, cognitive disorders, malnutrition or mobility impairment, and all were considered as "not frail" and apt to receive oncological treatment after the CGA and the implementation of CGA interventions. This is in line with the results of Kalsi et al[47] who showed an association between CGA interventions and improvement of chemotherapy tolerance in older cancer patients. Carrying out the CMR at the same time with CGA by a multidisciplinary team including

Table 4 Patient's Characteristics at Baseline According to Premature Systemic Treatment Discontinuation (n=169)

Variables	Premature Systemic Treatment Discontinuation				P value
	Yes (n=38)		No (n=131)		
	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	
Gender					
Male	27	(71.0)	69	(52.7)	0.04
Female	11	(29.0)	62	(47.3)	
Age					
70–74	11	(28.9)	25	(19.1)	<0.01
75–79	4	(10.5)	50	(38.2)	
80–84	16	(42.2)	30	(22.9)	
85 and over	7	(18.4)	26	(19.8)	
Cancer site					
Lung	15	(39.5)	37	(28.2)	0.02
Breast/Gynecologic	1	(2.6)	30	(22.9)	
Gastrointestinal	10	(26.3)	17	(13.0)	
Other	12	(31.6)	47	(35.9)	
ECOG-PS >2	12	(31.6)	31	(23.7)	0.32
G8 ≤14	34	(89.5)	115	(86.5)	0.68
ADL<6	12	(31.6)	46	(35.1)	0.68
IADL* <4	19	(50.0)	70	(53.8)	0.67
MMSE <24 (n=155)	6	(20.0)	23	(18.4)	0.84
GDS ≥1 *	6	(16.2)	31	(23.6)	0.33
Nutritional status					
Malnutrition #	16	(42.1)	43	(32.8)	0.29
Impaired handgrip strength##	16	(42.1)	48	(36.6)	0.54
Mobility					
TUG>20s (n=166)	15	(41.7)	50	(38.5)	0.72
OLBT < 5s (n=151)	23	(71.9)	74	(62.2)	0.31
Gait speed <0.8m/s (n=153)	10	(30.3)	31	(25.8)	0.60
Number of comorbidities *	3.1 ±2.0	[0–7]	3.7 ±2.6	[0–13]	0.17
Severe comorbidities**	13	(34.2)	58	(44.3)	0.27
Number of frailties	2.4 ±1.8	[0–5]	2.3 ±2.6	[0–5]	0.62
Biological status					
Renal failure (n=163)	3	(8.3)	4	(3.1)	0.17
Thrombopenia (n=164)	2	(5.6)	19	(14.8)	0.14
Lymphopenia (n=163)	6	(16.2)	23	(18.3)	0.77
Anemia (n=165)	13	(35.1)	50	(39.1)	0.66
Polymedication (≥5 drugs)	25	(65.8)	85	(64.9)	0.92
Identification of potential drug interaction *	20	(52.6)	52	(40.0)	0.16
Treatment					0.06
Mono-therapy	12	(31.6)	52	(39.7)	
Bi-therapy	25	(65.8)	62	(47.3)	
Tri or quadri therapy	1	(2.6)	17	(13.0)	
Grade 3–5 toxicities	13	(34.2)	11	(8.4)	<0.001

Notes: Anemia: Hb <11.5 G/dL Thrombopenia (<150 G/L) Lymphopenia: (<1.26G/L). #Malnutrition: BMI<21; Albumin <35g/L; MNA<17 - ## Impaired Handgrip strength: < 27 kg for men and < 16 kg for women. *1 missing value - ** 2 missing values.
Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; TUG, Timed Up and Go Test; OLBT, One-Leg Balance Test.

Table 5 Patient's Characteristics at Baseline According to Presence of Toxicities Grade 3–5 (n=171)

Variables	Toxicities Grade 3–5				P value
	Yes (n=24)		No (n=147)		
	N or Mean± ET	(%) or [min-max]	N or Mean± ET	(%) or [min-max]	
Gender					0.58
Male	15	(62.5)	83	(56.4)	
Female	9	(37.5)	64	(43.6)	
Age					0.31
70–74	6	(25.0)	31	(21.1)	
75–79	4	(16.6)	50	(34.0)	
80–84	7	(29.2)	40	(27.2)	
85 and over	7	(29.2)	26	(17.7)	
Cancer site					0.25
Lung	10	(41.7)	43	(29.3)	
Breast/Gynecologic	1	(4.2)	30	(20.4)	
Gastrointestinal	5	(20.8)	22	(15.0)	
Other	8	(33.3)	52	(35.3)	
ECOG-PS >2	7	(29.2)	36	(24.5)	0.62
G8 ≤14	21	(87.5)	128	(87.0)	0.95
ADL<6	6	(25.0)	52	(35.3)	0.32
IADL* <4	11	(45.8)	79	(54.1)	0.45
MMSE <24 (n=157)	6	(27.3)	23	(17.0)	0.25
GDS ≥1 *	2	(8.3)	35	(24.0)	0.08
Nutritional status					
Malnutrition#	8	(33.3)	51	(34.7)	0.89
Impaired handgrip strength##	11	(45.8)	55	(37.4)	0.43
Mobility					
TUG>20s (n=168)	7	(29.2)	58	(40.3)	0.30
OLBT < 5s (n=153)	11	(52.4)	88	(66.6)	0.20
Gait speed <0.8m/s (n=155)	5	(22.7)	37	(27.8)	0.62
Number of comorbidities*	3.7±2.7	[0–13]	3.5±2.4	[0–11]	0.74
Severe comorbidities**	14	(58.3)	59	(40.1)	0.09
Number of frailties	2.5±1.4	[0–5]	2.3±1.5	[0–6]	0.47
Biological status					
Renal failure (n=165)	1	(4.2)	6	(4.2)	0.98
Thrombopenia (n=166)	4	(17.4)	17	(11.9)	0.46
Lymphopenia (n=165)	4	(16.7)	25	(17.7)	0.90
Anemia (n=167)	5	(20.8)	59	(41.3)	0.06
Polymedication (≥5 drugs)	15	(62.5)	96	(65.3)	0.79
Identification of potential drug interaction *	11	(45.8)	63	(43.1)	0.80
Treatment					0.54
Mono-therapy	10	(41.7)	54	(36.7)	
Bi-therapy	13	(54.2)	76	(51.7)	
Tri or quadri therapy	1	(4.1)	17	(11.6)	

Notes: Anemia: Hb <11.5 G/dL Thrombopenia (<150 G/L) Lymphopenia: (<1.26G/L). #Malnutrition: BMI<21; Albumin <35g/L; MNA<17 - ##Impaired Handgrip strength: < 27 kg for men and < 16 kg for women. *1 missing value - ** 2 missing values.
Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; TUG, Timed Up and Go Test; OLBT, One-Leg Balance Test.

a clinical pharmacist,[55] in order to search potential DDI and avoid iatrogenia, can explain the lack of observed association between polypharmacy and systemic therapy discontinuation in our survey, as previously shown elsewhere.[56,57]

Associations between chemotherapy discontinuation and tumor site or chemotherapy regimen have already been reported.[45,52,58] In older cancer patients, lung and digestive cancers have worse prognoses than other cancers.[5] This may be one explanation for the highest frequency of chemotherapy discontinuation with these specific cancer localizations. Systemic treatment discontinuation is important in determining outcome of older patients treated for cancer as it is strongly associated with mortality in literature (in Fairfield et al[58]).

The present study has limitations. It was monocentric in design, including patients with all types of cancer and all types of systemic treatment. The heterogeneity of our study sample resulted in a lack of power for statistical analyses in subgroups of patients. Another difficulty was to perform CMR with the usual DDI tools (2012 Beers criteria and STOPP criteria), which are not designed for older people treated for cancer, and to take into account oncological systemic treatment. Finally, this is an observational study with no controlled group, and our results have to be confirmed in larger randomized studies.

The strengths of our study include new findings on outcomes in a population of older patients with initially adapted oncological treatment. Furthermore, few studies to date have incorporated concurrent CGA and CMR and evaluated the impact of these two assessments on oncological treatment decision-making and on older patients' outcomes. This multidisciplinary cooperation (oncologists, geriatricians and pharmacists) reflects the routine practice of the Coordination Unit for Geriatric Oncology in PACA West since 2017. Our findings highlight that this collaboration should be more largely considered in future clinical practice.

Conclusion

Older patients have frequent comorbidities, frailties and associated polypharmacy, exposing them to a high medication risk. This risk is even higher in older adults with cancer receiving chemotherapy or targeted therapy and it may lead to interruptions in cancer treatment with negative consequences on patient survival. The systematic collaboration between oncologists, geriatricians and pharmacists is essential to implement a personalized care plan in geriatric oncology. In our survey, initial treatment dose adaptation following CGA and CMR had no significant impact on overall survival and reduced grade 3–5

toxicities in older adults treated for cancer. All grades of toxicity were lowered, and discontinuation rate was comparable to those reported in the literature among older cancer patients. This CGA and CMR association is a plus to avoid DDI and improve oncological treatment initial dose decision-making, leading to better tolerance of systemic treatment in older adults.

Data Sharing Statement

Patient consent did not allow public data to be shared. To abide by French law, all requests for data, whether for analysis verification or meta-analyses, must be addressed to the corresponding author.

Acknowledgments

Author Contributions

All authors made substantial contributions to the study's conception and design, acquisition of data, and analysis and interpretation of data. All participated in drafting the article or revising it critically for important intellectual content. All gave final approval for the version to be published and agreed to be accountable for all aspects of the work.

Disclosure

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