VIA MEDICA

ORIGINAL ARTICLE

Barbara Radecka[1], [2], Justyna Czech[2], Agnieszka Siedlaczek[3], Marcin Maczkiewicz[4], Agnieszka Jagiełło-Gruszfeld[4], Renata Duchnowska[5]

[1]Department of Oncology, Institute of Medical Sciences, University of Opole, Opole, Poland
[2]Tadeusz Koszarowski Cancer Center in Opole, Department of Oncology with Daily Unit, Opole, Poland
[3]Institute of Mathematics and Computer Science University of Opole, Opole, Poland
[4]Department of Breast Cancer and Reconstructive Surgery, Maria Skłodowska-Curie National Institute of Oncology, Warsaw, Poland
[5]Department of Oncology, Military Institute of Medicine, Warsaw, Poland

Chemotherapy compliance in elderly patients with solid tumors: a real-world clinical practice data

Address for correspondence:
dr hab. n. med. Barbara Radecka
Department of Clinical Oncology,
Tadeusz Koszarowski Regional Cancer
Center, Opole, Poland
e-mail: brad@onkologia.opole.pl

Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0009

ISSN 2450–1654

ABSTRACT

Introduction. Malignant tumors in elderly people are more than ten times more prevalent than in the younger population. The data on the compliance with chemotherapy in older cancer patients managed outside of clinical trials is scarce.

Material and methods. We retrospectively assessed 181 consecutive cancer patients aged 65 years or more who received systemic chemotherapy. The study aimed to examine chemotherapy compliance in a large series of elderly patients managed in routine clinical practice. We also investigated the ability to complete chemotherapy in relation to selected factors, such as tumor type, treatment setting and line, type of chemotherapy, presence of comorbidities, body mass index (BMI), an expected glomerular filtration rate, hemoglobin level (Hb), a neutrophil-to-lymphocyte ratio, and Eastern Cooperative Oncology Group performance status (PS).

Results. Thirty-three percent of patients did not complete an initially pre-defined chemotherapy plan. The main reasons were disease progression (20%) and unacceptable toxicity (10%). Independent factors related to premature treatment termination included a lower BMI, a lower Hb level, lower PS, and palliative (compared to currative) setting.

Conclusions. In conclusion, premature chemotherapy termination not related to disease progression is relatively rare in elderly patients and may be predicted with routinely used clinical parameters.

Key words: older patients, solid tumor, chemotherapy, real-world data

Introduction

Older age is the most potent single risk factor for developing a malignant solid tumor. Over 80% of solid tumors are diagnosed in patients over 55 years of age, and 60% in patients over 65 years of age [1]. Malignant solid tumors in patients over 65 years are more than ten times more prevalent than in younger people [2]. Chemotherapy is the principal systemic anticancer treatment modality. Clinical trials indicate that the efficacy of chemotherapy is not related to age, however, treatment-related toxicities are more prevalent in older patients [3–6]. With advancing age, the number of comorbidities and related multiple medications increase. Aging of the society leads to an increasing proportion of older patients, including those with healthy lifestyles and not burdened with significant morbidities. In consequence, the life expectancy in Europe is estimated to exceed 80 years [7]. Physiological changes in the elderly lead to the functional impairment of the digestive tract, cardiovascular system, kidneys, and numerous abnormalities (neurological, emotional and cognitive,

Received: 10.12.2021 Accepted: 10.12.2021 Early publication date: 12.09.2022

immunological, and hematological). As a result, older patients are more susceptible to complications of systemic anti-cancer treatments, particularly chemotherapy. Traditionally elderly patients were underrepresented in pivotal clinical trials due to the risks of increased toxicities and related lower compliance rates. This approach has changed since the early 1990s, nevertheless, the proportion of elderly patients in clinical trials has remained lower than in the general cancer patient population [8–10]. Oncogeriatric evaluation tools facilitate a systemic treatment eligibility assessment [11–14] but have not been widely adopted in clinical practice. A real-life data on chemotherapy compliance in elderly patients managed outside of prospective clinical trials and on factors impacting compliance is still relatively scarce.

This study aimed to assess chemotherapy compliance in a large consecutive series of elderly patients routinely managed in a tertiary oncological center. We also investigated the ability to complete chemotherapy in relation to selected factors, such as tumor type, treatment setting, line and type of chemotherapy, presence of comorbidities, body mass index (BMI), an expected glomerular filtration rate (eGFR), hemoglobin concentration (Hb), a neutrophil-to-lymphocyte ratio (NLR), and the Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Material and methods

We retrospectively analyzed a group of 181 consecutive cancer patients 65 years of age or older, who were administered systemic chemotherapy for a year (from January to December 2019) at the Department of Oncology with Daily Unit, Tadeusz Koszarowski Cancer Center in Opole, Poland. Patient and treatment data were extracted from individual patient files. Patients who completed more than one line of treatment in the analyzed period were evaluated only for the initial treatment. The type of solid tumor, treatment setting (curative or palliative), the line of treatment, comorbidities, BMI, an eGFR, an Hb level, and a PS were recorded prior to treatment (Tab. 1). PS was evaluated using ECOG score [15]. Renal function was evaluated using eGFR (according to the Cockroft-Gault formula). The neutrophil-to-lymphocyte ratio (NLR) was calculated based on complete blood count. No primary prophylaxis against neutropenic fever with granulocyte-colony stimulating factor (G-CSF) was instituted and in a couple of cases, G-CSF was used as secondary prevention. Due to the retrospective type of our research no comprehensive geriatric assessment was available for these patients.

This study was approved by the Ethical Committee of the Regional Medical Chamber in Opole. All patient data were anonymized after being extracted from individual patient files, before analysis. The comorbidities were recorded as qualitative variables (0 — no significant comorbidities, 1 — diabetes, diabetes with coexisting cardiovascular disease or other, 2 — cardiovascular disease coexisting with other comorbidities but not with diabetes mellitus, 3 — other significant comorbidities not coexisting with cardiovascular disease or diabetes mellitus). Diabetes mellitus was singled-out as a condition that determines both the renal and microcirculatory statuses, and thus having a much broader systemic effect.

For treatment with curative intent, the number of planned chemotherapy cycles was set in accordance with relevant and current standards of care. The treatment plan for palliative treatment included at least eight chemotherapy cycles given every two weeks, or at least six chemotherapy cycles (four for lung cancer) administered every three weeks. No intended upfront dose reductions were applied. The ability to complete the pre-planned treatment schedule was considered as treatment compliance.

Treatment intent was categorized as follows: 0 — curative treatment, 1 — the first line of palliative treatment, 2 — the second line of palliative treatment, 3 — the third and subsequent lines of palliative treatment. Treatment-related toxicity was assessed in accordance with the Common Terminology Criteria of Adverse Events v 4.0 [16]. The reasons for not completing the treatment plan were classified as follows: 1 — disease progression (PD), 2 — unacceptable toxicity, 3 – health deterioration or other factors not related to cancer progression. Age, sex, type of malignancy, treatment aim (curative or palliative), palliative treatment line (first or later lines), comorbidities, BMI, and an eGFR were included in the analysis.

For continuous variables, the Mann-Whitney-Wilcoxon's test was used, and the qualitative variables were analyzed with Fisher and chi-squared tests. Multivariate analysis was performed using a logistic regression model. The following models were considered: a model with all considered variables, a model with each variable analyzed individually, and a model using the step method selected in the R program in accordance with the Akaike information criterion (AIC). To select the variables appropriately, statistical significance tests based on Wald's statistics were used.

Results

The median patient age was 71 years (range 65-88), and 45 patients (25%) were aged 75 years or older (Tab. 1). The majority of patients presented with a PS 0 or 1. More than 70% of patients were overweight or obese. Due to the small sample size, underweight patients were analyzed together with those with normal weight (as any

Table 1. Patient characteristics

Variables	N = 181	%
Age		
median	71	
range	65–88	
(65–< 70)	70	38.7
(70–< 75)	66	36.5
(75–< 80)	33	18.2
(≥ 80)	12	6.6
Sex		
male	94	51.9
female	87	48.1
Bodyweight		
median	73.1	
range	47.0–115.0	
BMI		
median	27.7	
range	16.3–40.6	
underweight or normal (< 25)	53	29.3
overweight (25–< 30)	67	37.0
≥ 30	61	33.7
ECOG-PS		
0	59	32.6
1	103	56.9
2	19	10.5
eGFR (mL/min)		
median	83.1	
range	29.3–162.1	
< 60	24	13.3
60–< 90	83	45.9
≥ 90	74	40.9
Hb level (g/dL)		
range	8–16.9	
< 10	11	6.1
≥ 10–N	90	49.7
N	69	38.1
> N	11	6.1

Table 1 cont. Patient characteristics

Variables	N = 181	%
Comorbidities		
no significant comorbidities	35	19.3
diabetes or diabetes with coexisting cardiovascular disease or other comorbidities	28	15.5
cardiovascular disease coexisting with other comorbidity but not with diabetes mellitus	102	56.4
other significant comorbidities excluding cardiovascular and diabetes mellitus	16	8.8
Cancer type		
colorectal	81	44.8
breast	42	23.2
lung	14	7.7
gastric	10	5.5
prostate	10	5.5
other	24	13.3
Treatment setting		
curative	47	26.0
palliative	134	74.0
Line of palliative treatment (N = 134)		
first	70	52.2
second	44	32.8
third or higher	20	14.9
Type of chemotherapy		
single-agent	69	38.1
combination	112	61.9

BMI — body mass index; ECOG-PS — Eastern Cooperative Oncology Group performance status; eGFR — expected glomerular filtration rate; Hb — hemoglobin concentration; N — normal values range female 12–14 g/dL, male 14–16 g/dL

significant skew in distribution was unlikely). The abnormal renal function (eGFR < 60 mL/min) was diagnosed in 13% of patients. Nearly half of patients presented with anemia, including 6% with a Hb level of 10 g/dL or less. The median NLR in the whole study cohort was 2.6, and 87% of patients had leucocyte and neutrophil levels within reference ranges. The most common malignancies were colorectal and breast cancers (45% and 23%, respectively). Three-fourth of the patients were treated with palliative intent, and the remaining patients received adjuvant treatment. Among those treated in the palliative setting, 52% received first-line treatment, 33% second-line, and 15% third- or subsequent lines. In all patients, chemotherapy was initiated at standard doses, according to the body surface area.

Treatment was not completed as planned in thirty-three percent of patients (Tab. 2). The most common reason was disease progression (20%), followed by unacceptable toxicity (10%). Major toxicities leading to premature treatment termination included dehydration and dyselectrolytemia related to uncontrollable diarrhea, oral cavity mucositis restricting adequate nutrition, and hematotoxicity. Grade 4 adverse events occurred in 13% of patients. There were no treatment-related deaths. Five patients (2.8%) stopped therapy prematurely due to a significant deterioration of overall health status not accompanied by apparent treatment-related adverse events or progression. Two of these patients presented with persistent significant fatigue, depression, and lack of appetite. Three patients did not show up for their scheduled visits, two necessitated in-patient treatment and one was lost to follow-up. In the univariate analysis, factors associated with premature treatment termination included a lower body mass and lower BMI, a lower eGFR, a lower Hb level, and an increasing chemotherapy line (Tab. 3).

Patients who completed the treatment schedule had a significantly higher BMI, a higher Hb level

(> 9.8 g/dL except for one patient), and a higher eGFR (Fig. 1). None of the four underweight patients was able to complete the scheduled treatment (two due to PD, and another two due to treatment-related toxicities).

We also conducted a univariate analysis of quantitative variables of more than two categories and those that differed significantly between the study subgroups that were able and were unable to complete the planned treatment schedule (Fig. 2). The treatment schedule was more often completed in a curative compared to a palliative setting (94% and 58%, respectively) and in those with a good ECOG-PS at baseline (Tab. 3, Fig. 2).

The stepwise multivariate analysis of risk factors for not completing treatment included BMI, an ECOG-PS, an Hb level, an eGFR, and a chemotherapy line. Body mass was not considered due to its close correlation with BMI.

The PS, the Hb level, and treatment line were statistically significant at the 90% confidence level, therefore, they were included in the final model. In addition, in accordance with the AIC, despite the lack of significance in the model using all variables, the BMI was also included, as it showed significance in the univariate model and the model selected by the step method. The coefficients obtained in the model define the influence of selected variables on the chance of implementing the treatment plan. A higher BMI and a higher Hb level were positive predictors of treatment completion, i.e. an increase in BMI by one unit and the Hb level by 1.0 g/dL increased the chance of treatment completion by 9% and 36%, respectively. In turn, increasing the PS

Table 2. Reasons for treatment non-completion and severity of adverse events

Variables	N = 181	%
Treatment		
completed	121	66.9
not completed	60	33.2
Reasons for treatment non-completion (N = 60)		
progression of disease	37	20.4
unacceptable toxicity	18	9.9
general health status deterioration	5	2.8
Adverse events severity (N=174)		
1	69	38.1
2	44	24.3
3	37	20.4
4	24	13.3

Table 3. Completion of planned treatment according to clinical factors

Variable	Treatment not completed n = 60	Treatment completed n = 121	p-value
Sex			
female	30 (34%)	57 (66%)	0.8347
male	30 (32%)	64 (68%)	
Age (years)	72 (65–83)	70 (65–88)	0.0512
Bodyweight (kg)	69 (47–102)	76 (47.7–115)	0.0007
BMI (kg/m2)	27.0 (16.3–37.4)	29.1 (20.7–40.6)	0.0073
ECOG-PS			
0	10 (17%)	49 (83%)	0.0001
1	37 (36%)	66 (64%)	
2	13 (68%)	6 (32%)	
eGFR	73.1 (35.6–162.1)	87.5 (29.3–139.9)	0.0015
Hb level (g/dL)	12 (8.5–16.9)	13 (8–16.6)	0.0004
Treatment setting			
curative	3 (6%)	44 (94%)	0.00001
palliative	57 (42%)	77 (58%)	
Type of chemotherapy			
single-agent	27 (39%)	42(61%)	0.2383
combination	33 (29%)	79 (71%)	
Absolute lymphocyte counts	1.76 (0.7–4.4)	1.89 (0.88–5.93)	0.4704
Perc1entage of lymphocytes	23 (7–50.9)	27 (9–53)	0.0106

BMI — body mass index; ECOG-PS — Eastern Cooperative Oncology Group performance status; eGFR — expected glomerular filtration rate; Hb — hemoglobin concentration

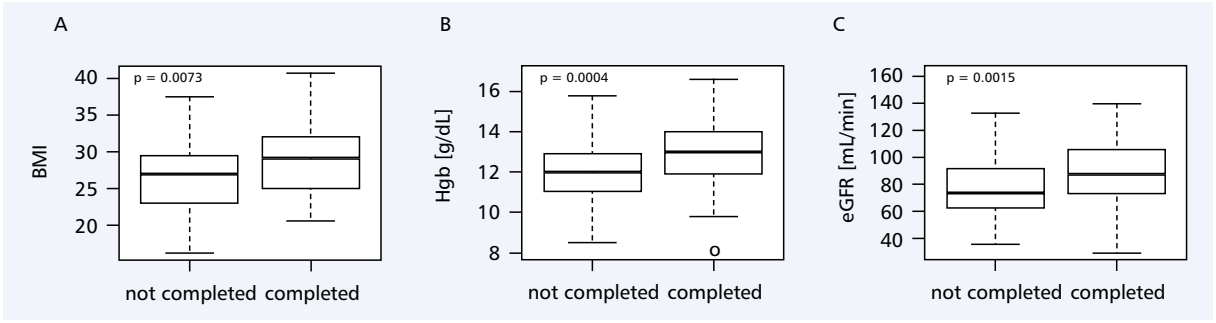

Figure 1. Treatment plan completion by body mass index (**A**), the hemoglobin concentration level (**B**), and the expected glomerular filtration rate (**C**); BMI — body mass index; eGFR — expected glomerular filtration rate

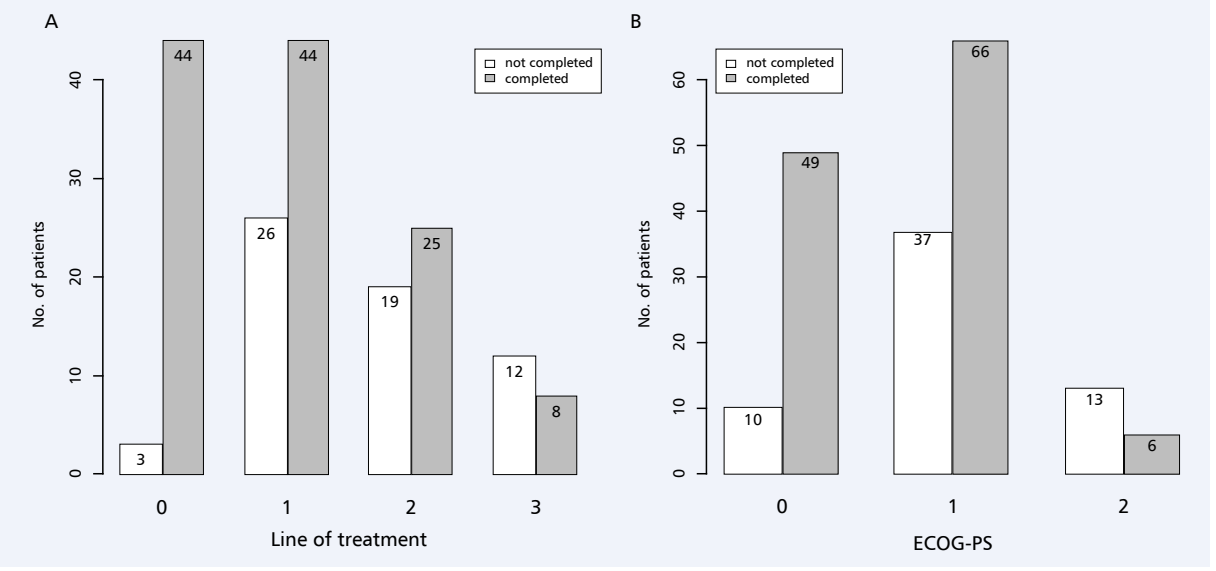

Figure 2. Treatment plan completion by line of treatment (**A**: 0 — currative treatment; 1, 2 i 3 — lines of paliative treatment) and by the Eastern Cooperative Oncology Group performance status (**B**)

and line of chemotherapy by one decreased the odds of treatment completion by 56% and 58%, respectively.

We also evaluated the occurrence of treatment-related toxicities in relation to all studied variables. Due to their small number, patients were divided into none/mild (CTC grade 0–2) and severe (CTC grade 3–4) adverse events groups. Severe adverse events occurred almost twice more often in PS 2 patients (58%) compared to those with PS 1 and PS 0 (31% and 31%, respectively; Tab. 4).

Severe adverse events were more frequent in patients with gastric (70%) and prostate cancers (60%) than in those with colorectal (23%), breast (29%), and lung cancers (36%). Severe adverse events were more frequent in patients with the eGFR <60 ml/min (50.0%) compared to those with the eGFR between 60 and < 90 mL/min and 90 mL/min or more (37% and 24 %, respectively).

Discussion

Many studies show that chemotherapy in elderly patients is equally effective, but sometimes more toxic. Every 5 years after the age of 65, the patient's chance of undergoing planned oncological treatment is significantly reduced.

Adherence to systemic therapies in elderly patients has been a matter of several studies, but factors influencing the ability to complete treatment have been analyzed only occasionally. For example, in a systematic review of the literature including 18 studies, the treatment adherence rate varied from 52% to 100%, but only one qualitative study asked older adults about reasons for non-adherence [17]. In consequence, factors influencing treatment compliance in elderly patients across particular studies remain inconsistent. Controversial factors include patient age of 75 years or more, comorbidi-

Table 4. Treatment toxicity according to selected variables

Variable	CTC G 0-2	CTC G 3-4	Total
ECOG-PS			
0	41 (69%)	18 (31%)	59
1	71 (69%)	32 (31%)	103
2	8 (42%)	11 (58%)	19
Cancer type			
colorectal cancer	62 (77%)	19 (23%)	81
breast cancer	30 (71%)	12 (29%)	42
lung cancer	9 (64%)	5 (36%)	14
gastric cancer	3 (30%)	7 (70%)	10
prostate cancer	4 (40%)	6 (60%)	10
other	12 (50%)	12 (50%)	24
eGFR (mL/min)			
< 60	12 (50%)	12 (50%)	24
61–90	52 (63%)	31 (37%)	83
> 90	56 (76%)	18 (24%)	74

ECOG-PS — Eastern Cooperative Oncology Group performance status; eGFR — expected glomerular filtration rate

ties, marital status, the need for hospitalization, general health condition, and communication abilities, to mention only a few. Most data hitherto have been collected within clinical trials, where the study population may be more motivated to complete the treatment compared with the general population, and our study is one of the few addressing this question in the real-world setting.

Inadequate knowledge on factors influencing chemotherapy compliance may result from different methods of data collection (administrative databases, clinical databases, or chart reviews) and a lack of relevant standardized guidance. For example, a review of 115 phase III trials in breast cancer demonstrated a large variability of reported outcomes, including relative dose intensity, number of cycles, dose modification, and early treatment discontinuation [18].

The prognostic value of age of cancer patients treated by chemotherapy has been a matter of many studies. The systematic review of 708 published papers on the effectiveness and safety of chemotherapy in older patients with colon cancer showed inconclusive data, with studies demonstrating better and worse outcomes in elderly populations [19]. However, grade 3 and 4 treatment-related toxicity in this study was related to age. Similarly, a multicenter review of 895 unresectable pancreatic cancer patients demonstrated no significant difference in survival of younger *vs.* older (> 65 years) patient treated by chemotherapy (333 *vs.* 274 days, respectively $p = 0.09$), and these results remained similar even when the age cut-off for older patients was increased to 70, 75, and 80 years [20].

In our study similarly to other series, BMI was found to significantly impact treatment compliance [4, 21]. In almost half of the patients, the baseline Hb level was below the normal value, including 5.5% of patients with Hb levels below 10 g/dL. As expected, a low Hb level was related to the inability to complete the planned treatment.

Recently, the prognostic value of NLR in cancer and other disorders, such as cardiovascular and infectious diseases, has been addressed [22]. Most studies show a higher NLR value in cancer (3.0) than in inflammatory diseases (1.97–2.5) [23–26]. We have not demonstrated any significant relationship between NRL and the ability to complete scheduled treatment. However, the majority of older patients in this series presented with normal levels of both lymphocytes and neutrophils.

We are aware of the limitations of this study, mainly due to its retrospective nature and patient heterogeneity. Additionally, the analysis of treatment compliance was based only on the ability to complete the planned number of cycles and did not include relative treatment intensity. Nevertheless, this data shed some light on chemotherapy compliance in elderly patients managed in routine practice. Notably, although around one-third of patients were unable to complete planned therapy, in two-thirds of instances treatment interruption was due to disease progression. Hence, age should not be considered a negative selection factor for chemotherapy if not accompanied by other adverse variables. Questionnaires such as Activities of a Daily Living, which assess the ability of a patient to independently care for basic needs like eating, washing, moving around, or the questionnaire called Instrumental Activities of Daily Living, evaluating patients ability to manage finances, do shopping, use a bus, phone, and take medications were shown to be useful in the assessment of the functional status [27]. In our series of factors related to premature treatment, termination included routinely measured parameters, such as BMI, the PS, or the Hb level. The

answer to the question of whether these predictors may be used instead of geriatric assessment scales remains to be established.

Conclusions

— A limited body of knowledge exists in fulfillment of chemotherapy, in elderly patients with solid tumors, outside of clinical trials. Thus, real-world data needs to be explored.
— We demonstrated the feasibility to predict chemotherapy failure in older patients using routinely measured parameters, such as BMI, eGFR, or hemoglobin concentration.
— We have shown that in the palliative setting, the ability to complete the therapy was impaired more often by the disease progression than treatment-related toxicities.
— Thus, our findings may be important in daily practice.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgements

The authors thank Prof. Jacek Jassem for critical review and scientific consultation of the manuscript.

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