Brief Report

Running Title: Futile Medication in Palliative Cancer Patients

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Futile Medication in Palliative Cancer Patients; a Report from the Middle East

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Abstract

Background: Palliative cancer patients suffer from a condition which needs to take many medications for supportive care and comorbid illnesses management. Therefore, they are at risk of drug-rated problems, such as futile medications. We aimed to discover the futile medication occurrence and identification as well as medication futility associated predictor factors.

Method: In a prospective cross-sectional study, we included patients with advanced/incurable malignancies admitted to Ala palliative clinic, a charity clinic affiliated to Omid hospital in Isfahan, Iran, between June 2018 and April 2019. To identify the use of fruitless medicine towards the end of life, we conducted a thorough analysis of the demographic information and prescription lists of terminally ill patients. The phrase "futile drugs" refers to those that are superfluous or redundant, have no significant benefits in terms of illness symptom management or survival time extension, or have a long-term chronic usage.

Results: From 133 involved patients, 114 (85.7%) were considered to use at least one futile medication (including only administration of unnecessary medications (70%) or both unnecessary and duplicate medication (30%). 35 patients were encountered with 48 medication duplications of the different pharmacological class of medications mostly opioids (33%). According to multivariate logistic regression analysis, the number of drugs and the average time to death were related with the prevalence of medication futility.

Conclusion: Palliative cancer patients were exposed to taking futile medications. More different prospective studies are warranted to evaluate the clinical and economic impact of futile medication use in oncology practice.
***Keywords**:* Cancer, Drug therapy, Medical futility, Palliative care

Introduction

For the past few decades, a debate has been rising among the medical, ethical and legal associations on the medical futility concept. The term "medical futility" refers to interventions that are unlikely to result in patient benefit or valuable therapeutic aims, and even have the potential for damage and resource waste.[1,2] However, a contemporary argument concerning medical futility rages when health care clinicians and patients (or family members) cannot agree on whether a certain therapy is futile or inappropriate/inadvisable for a patient's health state.[3,4] Uncertainty about the appropriateness of interventions was reported in terms of different perspectives of patients/families as well as clinicians on lifetime value. For example, the withdrawal of treatment, such as cardiopulmonary resuscitation and mechanical ventilation in critically ill patients was considered futile in several reports of critical ill patients.[5,6]

The medical futility was ethically challenged in terminally advance cancer patients in terms of the necessity of providing palliative care.[7,8] Integrating ethical principles play a crucial role in the implementation of unnecessary/futile interventions. A study of terminally ill cancer patients admitted to a palliative care unit (Princess Margaret Hospital in Toronto) revealed that 82 of 372 consecutive patients were receiving at least one useless medicine, of which 90% were needless medications and 10% were duplicate prescriptions.[3]

Mostly, advanced cancer patients are managed in an ambulatory setting, mainly home; however, they have the potential for encountering drug-related problems (DRP) such as taking futile medications in the ambulatory setting. Furthermore, we think that these patients' populations are the matter of DRP investigation especially in developing country such as Iran. We aimed to discover the futile medication occurrence and identification of the most important futile medications as well as the predictor factors in terminally ill cancer patients.

Materials and Methods

133 consecutive patients with advanced/incurable solid or haematological cancers who were hospitalized to Ala palliative clinic, a charity clinic connected with Omid hospital in Isfahan, Iran, between June 2018 and April 2019 were included in a prospective study of drug profiles. At Omid hospital, the advance cases of cancer who are not a candidate for curative treatment plan will be referred by their oncologists to palliative care center (Ala clinic) for symptoms and/or end-of-life management by exclusively trained physicians. These patients benefit from a home visit by Ala-clinic-related physicians.

The study protocol was approved by Isfahan University of Medical Sciences ethics committee (ID: IR.MUI.RESEARCH.REC.1398.166). Each participant has read and signed an informed consent form. We included all adult patients with solid or hematological malignancies who were hospitalized to the palliative care center and receiving only supportive treatment. Patients received at least two drugs from the category of oncological (not for curative purposes) or mostly non-oncological medicines were considered for data gathering.

During the last eight-month period, patients fulfilled the inclusion criteria according to demographic characteristics and diagnosis were screened for collection and analyses. Patients who were being considered to treat or re-challenging with of antineoplastic therapy and those who were unwilling to cooperate or had a great deal of missing information were excluded.

For data collection, the investigator compiled a list of all assigned patients to the palliative care clinic and conducted a thorough file review on patients' information, including demographics, cancer type, comorbidities, Charleston performance score, and drugs taken. During the time of follow-up until the patients' death, the overview on medications' profile was updated according to the newly prescribed medication or other non-prescribed over-the-counter medications or supplements in each home or non-home visit by the investigator. After

completing data collection for the aim of this research, two oncologists and one oncology clinical pharmacist from the Omid cancer hospital assessed the drug profile of each patient to determine if any medicine administered was ineffective.

The futile medication was defined as unnecessary or duplicate medication [3] and we considered the usefulness of each drug if it was used to manage a comorbid or baseline illness or a self-reported symptom. An unnecessary medication was defined as a medication which would not result in remarkable patient advantages in terms of disease's symptom control or prolonging survival time; those which suffered from scientific evidence for the purpose of administration (e.g., unproven alternative agents); or medications that had strong evidence for the indication of prescription but the goal of therapy was expected to happen only with the long-term chronic use (e.g., statins to treat hypercholesterolemia). Since our study had a prospective methodology, we were able to monitor the blood pressure and serum glucose level in order to find whether they were treated tightly. Because we believed that strict management had lost its benefits over a short period of time, we regarded any unneeded prescription for tight control of blood pressure or serum glucose level to be worthless. Duplicate medications were determined when two or more drugs from the same pharmacological class were being administrated in drug list of patient. The further assessment of medication therapy like appropriateness of drug dosage, frequency, schedule, and duration of therapy were beyond the scope of our study.

Continuous and categorical data were given as mean standard deviation or as a percentage (SD). Multivariate logistic regression was used to assess any potential relationships between the patients' age, sex, Charleston performance score, remaining time until death, amount of drugs administered, and type of cancer and the incidence of medical futility. *P* value of less than 0.05 was considered as statistically significant. Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

The summary of the demographic characteristics of enrolled patients was shown in table 1. The median age of patients was 64 ± 16.2 years (range 17–97 years), 40% were female, and gastrointestinal tumors were the most common. The most common pharmacological classes of medication used by patients were proton pump inhibitors (62% of patients), multivitamin supplements (44%), antipsychotic (42%), and opioids (41%). The mean number of medications was taking by advanced cancer patients were at least 13.5 medications (range 3–37). Diabetes (24% of patients), blood pressure (24%), cardiovascular diseases (21%), and thromboembolism (6.7%) were the most frequent comorbidities.

Among the 133 involved patients, 114 (85.7%) were considered to use at least one futile medication (including only administration of unnecessary medications (70%) or both unnecessary and duplicate medication (30%). There was no patient who was considered in futile medication category only due to duplicate medication prescription (Table 2).

Among the detected futile medications (N = 351), the administration of multivitamin supplements (47%), spironolactone (8%) aspirin (6.5%) and statins (5.4%) were the most reported. 11 (8.3%) patients with edema were taking albumin vial that was considered a futile medication and 11 (8.3%) and nine (6.8%) patients were objected to tight control of blood pressure and blood glucose, respectively. A total of 48 medicine duplications from various pharmacological classes were found in 35 patients, including 33% who were taking two distinct opioids, 25% who were taking two different corticosteroids, and 16% who were taking two different antipsychotics without any specific justification. According to the multivariate logistic regression analyses, number of medications used and mean survival days before death were the predictors of medical futility occurrences in the investigation (Table 3).

Although the methodology of the study was not interventional, discontinuation of several medications was recommended by the investigators' team.

Discussion

To the best of our knowledge, this is one of the first study evaluating the frequency and demographic correlates of medication futility in

the palliative cancer patients in Iran which also adds to the scarcely available evidence on this topic in palliative oncology field.

In Iran, a prominent referral cancer facility allowed us to evaluate prospectively the prescriptions for patients with terminal cancer who were there. We found that more than 85% of cancer patients receiving palliative care who are nearing the end of their lives use ineffective drugs, most often multivitamin supplements. Among demographic characteristics and clinical factors that we assessed, the number of medications used and the mean time of survival before death were associated with the occurrence of medication futility.

During the last few decades, progress in the supportive care of cancer patients has resulted in the improvement of the quality-of-life as well as the survival of these patients. Several studies have noted that many cancer patients continue to receive aggressive interventions, including chemotherapy, even the day before death.[3,9] Often terminally ill cancer patients were treated by numerous medications in order to manage comorbid illness and other cancer-associated symptoms.[10] Even there is a study in which increase in the number of medications was reported as death time approaches.[11]

However, such an increase in the number of medications used to manage cancer has expanded the risk of DRP such as medication futility, duplicate medications, adverse effects and even drug-drug interactions.[3,10,12]

During the literature review, we found that our range of patients who were exposed to futile medications (85.7%) in our center was much higher than similar studies.[3,13] For example, in a similar study conducted by *Riechelmann et al*. in 2009, from 372 assessed terminally ill cancer patients, 22% of them were encountered by medication futility that contained 70 patients with unnecessary medications and eight with duplicate medications.[3] The large number of futility reports in our research is likely attributable to cultural concerns in our country. At the end of life, Iranian patients, their carers, and health care personnel attempt to prolong the patients' lives while knowing it is futile. They would prescribe and administer whatever drug they believed to be beneficial, resulting in polypharmacy. In the meanwhile, such irresponsible polypharmacy might lead to drug-related issues such as medication futility.

On the other hand, there is a difference between unnecessary medication pharmacological class taken by the patients in our study and *Riechelmann et al*. study.[3] In their palliative care cancer center, statins (56%), lipid-lowering drugs, were determined to be the most class of medication with defined therapeutic indications and multivitamin supplements stood on a third place. However, we could show that near all of our palliative care patients were taken multivitamin supplements led to the high amount of medication futility report in our survey.

Despite the fact that the disparity might be ascribed to cultural factors owing to the Iranian population's hopeful view of the advantages of alternative therapies, there is an additional factor to consider. In the previous study,[3] in terms of the retrospective nature of methodology, the author was not able to meticulously assesse the over-the-counter medication and self- prescribed supplement; however, by aim of home visit follow-up in our study, we could confront the limitation and detect all medications that were taken by terminally ill cancer patients. From a physician's perspective, multivitamin pills would neither benefit nor damage their patients; additionally, refusing or adamantly insisting on not eating these supplements would not be a cause for worry among countless terminally sick cancer patients suffering comorbidity. These methods contributed to the reporting of multivitamin supplements as the first ineffective drug. Apparently, the multivitamins have not adverse clinical consequences, but they have potential of drug interaction[3] and can impose a cost burden to the family economic that should be considered.

Besides, study showed that physicians overestimate the survival time of cancer patients by up to 40% [15]; therefore, they tended to continue to prescribe futile medications in terms of the prognosis overestimation. In addition, clinicians may be hesitant to adversely impact patients' optimism by terminating drugs that have been used chronically or for which long-term administration is anticipated to elicit therapeutic advantages. The terminally sick cancer patients and their families suffer from a fragile psychological state, and even little modifications in their drug profiles might impair the patient-physician connection, their morale, and their tolerance.

In the previous studies, some other factors, such as lack of medication reconciliation, patient requests, lack of medical knowledge, the

reasonably desirable safety profile of drugs such as statins,[3,13] physician and patient belief in the potential benefits, lack of harm of the futile drugs, moral concern and recommendations from the other medical specialists were suggested as a potential reason for prescribing or continuing to take futile medications in terminally ill cancer patients.

The main limitation of study was the fact that this study was conducted in a single-institution without any interventional modalities. In contrast to other similar studies, however, patients were evaluated prospectively, and we were able to identify all prescribed and non-prescribed medications according to clinical condition and arrive at a precise estimate of futile medications at the end of life in cancer patients with terminal illness. Furthermore, we could estimate the severity of patients' comorbidity to evaluate the true need for pharmacological therapy, the inappropriate continuation of antihypertensive or hypoglycemic agents are particularly important in this regard. We believe that compared to previous study, [3] our estimation for taking futile medication is more reliable and close to reality in our country.

There was another strong point in our study, we analyze the possible relationship between occurrence of medication futility and demographic characteristics and clinical factors; in comparison with the study by Fede et al.[13] who have reported the Charlson comorbidity index ≤ 1 and drug reconciliation by physician as the risk factors for medication futility, we found that the more number of medications used and the longer survival time are two significant statistically factors for medication futility occurrence in terminally ill cancer patients. We believe that the influence of other factors, such as cultural and moral issues, physician choice, and patient desire, was much greater than that of demographic patient characteristics or even criteria such as performance status, cancer kind, and life expectancy.

The administration of futile medications in terminally ill cancer patients can be resulted in adverse drug events, diminishing treatment efficacy, reduced patient quality of life and waste the economic. Furthermore, continuous reassessment of patients' medication lists in order to find the logical reason for prescribing, continuing or discounting each medication in the terminally ill cancer condition is crucial. Health care professionals should make an effort to enhance their relationships with patients and their families in order to better comprehend why patients are urged to take ineffective drugs and what their emotional needs are. They should be required to consult with an end-of-life consulting clinic in order to progressively accept their situation.

Conclusion

In summary, the present report showed that more than 80% of terminally ill cancer patients were exposed by taking medications that lack benefit in the short-term or had no definite administration indication. More different prospective studies with population-based analyses are warranted to evaluate the clinical and economic impact of futile medication on oncology practice.

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Conflict Interest

None declared.

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Table 1. Demographic characteristic of enrolled patients

Patient characteristic (N=133)	No. of patients or value
Mean age (y), range	64.2 ± 16.2 (17-97)
Sex	
Female	79 (59.4%)
Male	54 (40.6)
Median days of survival until death, range	
	80.4 (3-363)
Cancer type	
Colorectal	
Stomach	22 (16.5%)
Brain	14 (10.5%)
Pancreas	13 (9.8%)
Breast	10 (7.5%)
Hematologic	8 (6%)
Bladder	8 (6%)
Others	8 (6%)
	50 (37.6%)
No. of comorbidities	
Diabetes	
Blood pressure	32 (24%)
Cardiovascular disease	32 (24%)
Thromboembolism	29 (21%)
Alzheimer	9 (6.7%)
Renal failure	8 (6%)
Hypothyroid	8 (6%)
Hyperlipidemia	8 (6%)
	8 (6%)
Mean No. of drugs prescribed per patient, range	
	13 (3-37)

Table 2. Futile medications used by the patients in details

Characteristic	Number (%)
No. of patients taking futile medications	114 (85.7)
Type of futile medication	
All	114 (100)
Unnecessary [1]	114 (100)
Duplicate	48 (42)
Unnecessary medications taken by patients	
All	351 (100)
Multivitamin supplements	166 (47)
Spironolactone	29 (8)
Aspirin	23 (6.5)
Statins	19 (5.4)
Others	114 (32.5)
Duplicate medications	
All	48 (100)
Opioids	16 (33)
Corticosteroids	12 (25)
Antipsychotics	8 (16)
Others	12 (25)

Table 3. Multivariable analyses for the factors associated with drug futility

Variables	Unadjusted OR (95% CI)	Unadjusted *P*-value	Adjusted OR (95% CI)	Adjusted *P*-value
Age	1.01 (0.98-1.04)	0.18	1.01(0.94-1.08)	0.72
Gender	0.56 (0.21-1.5)	0.25	0.52 (0.18-1.47)	0.22
Number of medication	1.31(1.12-1.53)	<0.001 Reference	1.51(1.17-1.95)	<0.001 Reference
Presence of comorbidity illness	1.25(0.82-1.93)	0.29	1.43(0.84-2.44)	0.17
Median days of survival until death	1.01(1.00-1.02)	0.02	1.01(1.00-1.03)	0.02
Type of cancer	0.97(0.93-1.02)	0.31	0.96(0.92-1.02)	0.22
Charlson comorbidity index	0.97(0.82-1.15)	0.76	0.90(0.73-1.12)	0.36

OR: Odds ratio; CI: Confidence interval