Markers of frailty in cancer treatment election: A case report.

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Abstract

Management of elderly oncology patients presents some difficulties when deciding if a patient is suitable for curative treatment or not. Apart from the tumour characteristics, there might be some other factors that influence in this decision, as previous illnesses, disability or general life expectancy. Standardized geriatric assessment must be applied in these cases, evaluating frailty in the elderly as one important prognosis factor, as it has been related to higher mortality and worst treatment tolerance.

As symptoms, signs and exploratory findings can have common characteristics both for cancer and frailty, it is necessary to find other paths for approaching the frailty diagnosis that may influence the kind of treatment that a cancer patient receives. Biochemical markers are being developed, but in most cases they are not specific for cancer or frailty. Cardiovascular risk of patient, taking account on the analytic evolution of cardiovascular risks factors in the years previous to the neoplasia diagnosis, can help in the evaluation of the patient´s prognosis.

DNA methylation pattern changes with age, and is also altered in cancer patients. This fact relates the apparition of cancer with aging. Further research must investigate on this subject, in order to identify possible methylation patterns that can discriminate frail cancer patients and non frail ones.

Introduction

Frailty is a complex syndrome related with the presence of adverse health outcomes [1] that appears in the 19-44% of adults over 65 [2]. It is present when the functional reserve of the different physiologic systems declines, so any damage to them makes loose the balance and provokes a disease. It is a way of defining the "biological age" of an individual, that can be different from its "chronological age" and it's a more acute tool for prognosis [1].

It can be measured by using scales that register physical parameters like gait speed, strength or aerobic resistance. Some of these validated scales are the *Short Physical Performance Battery* (SPPB), the Fried phenotype or the FRAIL scale. Nevertheless, there are no common standard for detecting or measuring frailty, as other proposed scales include disability or psychological disorders, like the one of the Canadian Study of Health and Aging (CSHA) [3].

Some biomarkers have been studied in order to correlate them to frailty. It has been demonstrated that higher levels of PCR or Tumoral Necrosis Factor α (TNFα) and decreased levels of Vitamin D and leucocytes are related to frailty. It shows that frailty has something to do not just with the general aging, but with molecular and biochemical changes that happen as the patient become elderly [4].

Cancer is an increasingly disease among older adults. The 60% of the new diagnosis of cancer is made in people over 65 years old, half of them over 75 [5]. In most cases, as both frailty and cancer are related to age, these entities can be present simultaneously in the same patient. It is important to study the way one influences the other and distinguish if the symptoms presented by a patient are secondary to the neoplasia or to frailty. Frailty status can modify the elected treatment for a patient [6].

Case Report

A 77 year old man reports a change in his intestinal habit since 3 months ago, presenting constipation that does not respond to laxatives as macrogol or lactulose. He also complains about abdominal pain, not well defined, intermittent and almost daily. He has a well-controlled hypertension and diabetes mellitus with HbA1c of 7%, and he smokes since he was 18. He receives treatment with enalapril 20 mg twice a day, metformine 850 mg every 8 h and vildagliptin 50 mg every 12 h.

A physical exploration demonstrates an increased size of the liver edge, with pain in the upper part of the abdomen without peritoneal irritation. Faecal occult blood is found and the exploration is completed by a colonoscopy. Finally, a colorectal tumour is diagnosed 23 cm far from the anal margin. Biopsy confirms the affection of muscularis. The axial tomography (TC) demonstrates the presence of 1 metastasis in liver with two centimetres of diameter.

Geriatric assessment is ordered from Primary Care to assist oncologists about the general conditions of the patient, so they can decide which treatment fits better for him. He obtains a Minimental (MMSE) punctuation of 25 (normal), a normal Yesavage test for depression and he is independent for instrumental daily life activities. Once it has been demonstrated the good patient status, oncologist decide treatment. First, metastasis was chemoembolized, and tumour was extracted after neoadjuvant chemotherapy. Patient received chemotherapy after surgery too and remained free of illness for four years. Blood tumour markers were normalized within a few months, as well as PCR and albumin.

In these years, and as a consequence of peripheral neuropathy, he developed a skin ulcer in right talus, with secondary decreased mobility and loss of muscle mass. Slowly, PCR levels increased to 25 mg/dl, as well as low albumin levels were recorded. Diabetes control became difficult, with HbA1c levels of 8%. Blood tumour markers remained stable. When the patient was 81, levels of carcinoembryyonic antigen (CEA) increased in blood, what led to deeper examination, detecting through colonoscopy a tumour recurrence, with three lesions in liver corresponding with metastasis. PCR increased from 25 mg/dl to 60 mg/dl and blood proteins decreased.

Just before the recurrence diagnosis, the patient had a slow gait speed, couldn't achieve getting to a second floor through the stairs and had to stop every 50 m. Furthermore, after initial chemotherapy Chronic Obstructive Pulmonary Disease (COPD) was diagnosed in the patient and also chronic heart failure (NYHA class II) probably related to cardiovascular risks factors and chemotherapy induced cardiac harm. Frailty was established following FRAIL scale. A Primary Care nurse worked with the Family Physician in the management of the complex patient´s situation, in terms of periodic control of its cardiovascular risk factors, counselling and support, increasing the knowledge of the patient and his family about his diseases. Although the patient had a good response to surgery and chemotherapy previously, frailty condition made not recommended curative treatment. Nevertheless, evaluating real possibilities for complete recovery needed again a complete geriatric assessment. The patient had

become dependent for some daily live activities such us bathing or dressing up, with punctuation on Barthel test of 60 points. No symptoms of depression were found, but MMSE decreased to 18.

Due to the shortened life expectancy because of frailty and other comorbidities, and the increased possibility of adverse health outcomes secondary to cancer treatment, he received palliative treatment after discussing the options and according to medical counselling, achieving three years with good quality of life.

Discussion

As elderly population is increasing, as well as cancer prevalence in people over 65 [5], we need to evaluate the real options of each patient of coping with cancer treatment, not only in terms of survival, but also related to side effects of treatments [6]. These options depend on cancer stage, kind of tumour and possible therapies [7], but also in the personal status of the patient previously to the appearance of the neoplasia. It is necessary to have an approximated idea of the patient's life expectancy, in order to establish if it is logical to prescribe a treatment with curative intention or a palliative one [6]. Frailty appears as a useful tool to advice on the general status of a patient, as people from the same age can have very different health status. It has been related to a higher rate of adverse health outcomes, like mortality, bad response to treatment or presence of side effects. Frail patients have a short life expectancy too and that is why it is an important parameter that must be checked for deciding treatment strategies [8]. The action of care managers that help patient´s to understand and control their chronic diseases might be useful in order to prevent the apparition of frailty syndrome and/or detect it in early stages. The Table 1 of the care manager appears as a way of focusing the health care action in the patient, enabling him to manage his chronic conditions and improve his health [9].

Some studies remarked that older patients with colorectal [10], urologic [11] or any other kind of cancer [12] had more risk of mortality and presence of intolerance or chemotherapy side effects than non-frail. These works were based on phenotyipic definitions of frailty, although some used also definitions that include disability. Nonetheless, cancer patients may have symptoms due to their disease or as side effects of treatment that can overlap with frailty symptoms and signs, as slow gait speed, weight loss or low strength. In order to distinguish them, there are two factors that are important: first, knowing the previous health level of the patient, before de appearance of cancer. In this aspect, the collaboration of the Family Physician is crucial, as he

Table 1. Principal frailty diagnostic tools [3,4,17]

Tools that part from physical examination and anamnesis	Blood parameters related to frailty	Possible future tools
FRAIL scale	PCR	Markers of cardiovascular risk: HbA1c, LDL
Frailty Index	IL6	DNA methylation pattern
Groningen Frailty Index	Proteins/albumin	
CSHA	Neutrophils	
	TNF α	

usually knows the patient, its environment and its evolution through time [13]. Second, it could be reasonable to develop blood markers of frailty. Levels of these biochemical markers must be compared with the ones considered normal for each population [4]. Some of them will be summarised in order to check the current status of the question.

In the field of biochemical markers for frailty there is work done, but it is in an early development stage. We already know that inflammation markers as PCR are elevated in frail patients. This kind of markers is not useful in cancer patients as they also increase due to this illness. Other studies have demonstrated an increased level of neutrophils, TNFα and interleukin 6, but these parameters have the same limitations as PCR. Decreased levels of blood proteins like albumin, and also of lymphocytes have been found in frail patients. Apparently, there is also a loose of balance between undifferentiated T Cells and memory T Cells, with less proportion of the lasts. Androgen levels must be low, as other proteins and hormones like as myokines. But all these alterations can be found in a non-frail patient with a neoplasia, so they are not useful for building a prognosis model in these cases [14].

Levels of vitamin D have a direct relationship with frailty, adverse health outcomes and mortality, as well as falls [15]. This marker might be useful in order to improve patient´s probability of survival, although further research of its implications in cancer must be developed. Frailty is related with cardiovascular risk, so it is common to find glucose intolerance, diabetes or dyslipemia in frail people [16]. Frail patients have a higher glucose level in blood, and other parameters related to atherosclerosis. Sometimes, the medical action in an oncology patient is centred just in the neoplasia treatment, but if the patient is elderly it is also important to control his cardiovascular risks linked to frailty and chemotherapy side effects. Studies must be developed in order to describe, if existing, the relationship between biochemical markers for cardiovascular risk and frailty, as well as between them and cancer prognosis. This way, maybe we can find some other biochemical markers for frailty in cancer patients, mostly by using complex indexes [14].

There are other possible strategies to assist in cancer treatment apart from describing the patient's phenotype before diagnosis, although they must be developed. Genetics and epigenetics changes related to aging can be a future path for this purpose. DNA methylation controls the transcription of the genoma, mostly by silencing the transcription of some genes. This pattern changes with time, influenced by environmental and genetics factors, and is involved in cancer development, as well as in aging. DNA methylation pattern can be analyzed in order to get a "methylated DNA age" or "epigenetic age" that can be different from the chronological age of the subject. This epigenetic clock is a better predictor for disease and mortality than chronological age [17].

It is known that DNA methylation influences the appearance of cancer and the resistance to some treatments [18]. An example is the HER2 receptor in breast cancer. The study of different methylation patterns in an elderly oncology patient might be the key to personalised treatments [19], solving the problems of low specificity of actual patterns (symptoms, signs, biochemical findings…) of frailty. Perhaps, in a not so distant future, the calculus of the epigenetic age may be used as a predictor of response to treatment, helping doctors to decide not only which chemotherapy agent use, but also if the intention of treatment will be curative or palliative. This will give the patient the power to organise his life plan, respecting his dignity and organise his treatment more globally.

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