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Immune senescence and cancer in elderly patients: Results from an exploratory study☆

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ABSTRACT

Background: The challenge of immune senescence has never been addressed in elderly cancer patients. This study compares the thymic output and peripheral blood telomere length in ≥70 year old cancer patients.
Patients and methods: Fifty-two elderly cancer patients and 39 age-matched controls without personal history of cancer were enrolled. All patients underwent a Comprehensive Geriatric Assessment (CGA), from which a multidimensional prognostic index (MPI) score was calculated. Peripheral blood samples were studied for naïve and recent thymic emigrant (RTE) $CD4^+$ and $CD8^+$ cells by flow cytometry. T-cell receptor rearrangement excision circle (TREC) levels, telomere length and telomerase activity in peripheral blood cells were quantified by real-time PCR.
Results: The percentages of $CD8^+$ naïve and $CD8^+$ RTE cells and TREC levels were significantly lower in cancer patients than in controls ($p = 0.003$, $p = 0.004$, $p = 0.031$, respectively). Telomere lengths in peripheral blood cells were significantly shorter in cancer patients than in controls ($p = 0.046$) and did not correlate with age in patients, whereas it did in controls ($r = -0.354$, $p = 0.031$). Short telomere (≤median)/low TREC (≤median) profile was associated with higher risk of cancer (OR = 3.68 [95% CI 1.22–11.11]; $p = 0.021$). Neither unfitness on CGA nor MPI score were significantly related to thymic output or telomere length in either group.
Conclusions: Immune senescence is significantly worse in elderly cancer patients than in age-matched controls. The low thymic output and the shorter telomeres in peripheral blood cells of cancer patients may reflect a pre-existing condition which facilitates the onset of malignancies in elderly people.

1. Introduction

People over 65 years old are the fastest-growing age bracket in the population and will account for an estimated 20% of Americans and 25% of Europeans by the year 2030 (Fries, 2003). The incidence of malignancies increases with age, so the number of cancers in the elderly is expected to increase significantly in years to come (American Cancer Society, 2012). Several studies have shown that elderly patients are less likely to be treated according to guidelines, and their under-treatment may be detrimental to both survival and quality of life (Bouchardy et al., 2003; Dale, 2003; Ng et al., 2005; Sargent et al., 2001). Elderly cancer patients may benefit from chemotherapy just as much as younger adults, but at a higher risk of hematological toxicity (Hurria et al., 2012; Muss et al., 2005, 2007). A better understanding of the physiological and functional changes that occur with aging will enable us to improve strategies for treating elderly cancer patients. Since the aging process coincides with a gradual decline in the functional reserve of multiple organ systems (Balducci, 2003) the search for laboratory markers of biological aging and organ reserve should be a priority of clinical research in the field of geriatric oncology.

Over a lifetime, the immune system undergoes a profound remodeling process with major impact on health and survival (Fulop et al., 2010; Grubeck-Loebenstein et al., 2009). Thymic involution and diminished

Abbreviations: CGA, comprehensive geriatric assessment; MPI, multidimensional prognostic index; RTE, recent thymic emigrant; TREC, T-cell receptor rearrangement excision circle; RU, relative units; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SPMSQ, Short Portable Mental Status Questionnaire; MMSE, Mini Mental Status Examination; CIRS-CI, Cumulative Illness Rating Scale-Comorbidity Index; CIRS-SI, Cumulative Illness Rating Scale-Severity Index; GDS, Geriatric Depression Scale; MNA, Mini Nutritional Assessment; T/S, telomere/single-copy gene; PBMC, peripheral blood mononuclear cells; CMV, Cytomegalovirus.

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output of T lymphocytes are thought to be among the major factors contributing to the loss of immune function with age (Berzins et al., 1998). T cell output begins to decline exponentially from early in life, and at 75 years of age the immune repertoire appears to be severely impaired (Douek et al., 1998; Naylor et al., 2005). However, recent data suggest that the thymus may remain active even late in life, supplying functional T cells to the periphery (Mitchell et al., 2010; Nasi et al., 2006).

Measuring T cell receptor rearrangement excision circle (TREC) levels in peripheral blood lymphocytes has been suggested as a method for quantifying thymic output (De Rossi et al., 2002; Douek et al., 1998; Ometto et al., 2002; Zhang et al., 1999). TRECs are generated by T cell receptor gene rearrangement and maintained in thymic emigrant cells as DNA episomes. Because TRECs are not duplicated during mitosis, their concentration is diluted out with each cell division. The frequency of recent thymic emigrant (RTE) cells in peripheral blood, identified by the marker $CD31^+$ among $CD45RA^+$ naïve T cells (Kimmig et al., 2002), decreases with aging and correlates well with the decline in TREC levels (Junge et al., 2007; Kohler et al., 2005). Very little is known about the relationship between TRECs and cancer, especially in elderly patients. One study on head and neck cancer patients, including only a few ≥70 years old, showed that the age-associated decrease of TREC numbers and naïve T lymphocytes was significantly greater in cancer patients than in controls, suggesting altered lymphocyte homeostasis in the former (Kuss et al., 2005).

The immune system function depends largely on its capacity for extensive cell division and clonal lymphocyte expansion. Telomere length and its regulation by telomerase have attracted considerable attention, due to their potential roles in controlling cell replication (Blackburn et al., 2006). Telomeres are capping end structures of eukaryotic chromosomes essential for protecting chromosome integrity (Blasco, 2005). Telomeres are progressively shortened during each cell division due to end-replication problems of DNA polymerase; when a critical length is reached, the cell undergoes cycle arrest and apoptosis (Blasco, 2005). Permanent cell growth relies on telomere maintenance, and certain human cell subsets, as well as most cancer cells, have telomerase activity which enables telomere elongation (Dolcetti and De Rossi, 2012). Despite their telomerase activity, most tumor cells have shorter telomeres than the corresponding normal tissues, and there is a relationship between short telomeres and genetic instability (Garcia-Aranda et al., 2006; Rampazzo et al., 2010). Since telomere shortening reflects cell turnover and exposure to oxidative and inflammatory damage, which are crucial processes in biological aging, it has been suggested that telomere length serves as an indicator of aging (Aviv, 2006; Baird, 2006; Wong and Collins, 2003). Telomere shortening in peripheral blood cells has been associated with a number of chronic diseases, such as coronary heart disease, hypertension, dementia, obesity, insulin resistance, and osteoporosis. However, two clinical trials failed to confirm any relationship between telomere length and frailty syndrome in elderly non-cancer patients (Collerton et al., 2012; Woo et al., 2008).

Several studies have investigated the relationship between telomere length in peripheral blood cells and cancer risk. Although few manuscripts report that longer telomere length is a risk factor (e.g. Lan et al., 2013; Svenson et al., 2008), most of the studies indicate that short telomere lengths are associated with a higher cancer risk (Bojesen et al., 2013; Martinez-Delgado et al., 2012; Riegert-Johnson et al., 2012; Shao et al., 2007; Wu et al., 2003). To date, however, telomere length in peripheral blood cells has been measured in elderly non-cancer patients and younger cancer patients, but no data are available for elderly cancer patients. We present here the results of a prospective observational study providing the first description of immune senescence markers and frailty scores in elderly cancer patients and age-matched controls.

2. Material and methods

2.1. Study design and study population

Patients enrolled in this study were aged ≥70 years, with stages I–III breast or colorectal cancer, diagnosed during the previous 2 months and radically resected, consecutively admitted to the Medical Oncology Units from September 2010 to March 2012. Controls included patients ≥70 years old with no personal history of cancer, consecutively admitted to the Geriatric Clinic. For both groups, the exclusion criteria were: any hematological disorders, chronic diseases requiring immunosuppressive treatment, prior immunodeficiency, blood transfusion ≤4 weeks before blood sampling, active infectious diseases, extremely severe comorbidities suggesting a life expectancy <6 months, or severe cognitive impairment hampering communication with the physician. The study was approved by the institutional Ethics Committee and conducted in accordance with the Helsinki Declaration and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

2.2. Clinical assessment

Complete demographic and clinical details were collected at baseline for each patient (Table 1). At the first visit, both cases and controls underwent traditional comprehensive geriatric assessment (CGA)

Table 1
Demographic and clinical characteristics of cancer patients and controls.

	All patients, *n* (%)	Cancer patients, *n* (%)	Controls, *n* (%)
Age (yrs)			
n	91 (100)	52 (57.2)	39 (42.8)
Median, range	81, 70–92	81, 72–92	80, 70–91
Gender			
Male	26 (28.6)	19 (36.5)	7 (17.9)
Female	65 (71.4)	33 (63.5)	32 (82.1)
Performance status (ECOG)			
0–1	83 (91.2)	51 (98.1)	32 (82.1)
≥2	8 (8.8)	1 (1.9)	7 (17.9)
Social condition			
Home	90 (98.9)	51 (98.1)	39 (100)
Nursing home	1 (1.1)	1 (1.9)	0 (0.0)
Type of assistance			
Alone	23 (25.3)	9 (17.3)	14 (35.9)
Family	59 (64.8)	38 (73.1)	21 (53.8)
Others	9 (9.9)	5 (9.6)	4 (10.3)
Caregiver assistance (hours/day)			
Median time, range	24, 2–24	24, 2–24	24, 3–24
Tumor stage (TNM)			
I	–	16 (30.8)	–
II	–	33 (63.5)	–
III	–	3 (5.7)	–
Modality of diagnosis			
Symptoms/self examination	–	40 (76.9)	–
Screening	–	9 (17.3)	–
Incidental diagnosis	–	3 (5.8)	–
Therapeutical choice			
Adjuvant therapy as for younger adults	–	31 (59.6)	–
Adapted treatment	–	18 (34.6)	–
No adjuvant therapy	–	3 (5.8)	–
Agreement to proposed therapy			
Ready	–	51 (98.1)	–
Patient refusal	–	1 (1.9)	–
Cause of admission to hospital/ outpatient services			
Cardiovascular disease	–	–	18 (46.2)
Peripheral deep venous thrombosis	–	–	4 (10.2)
Gastrointestinal inflammatory disorders or bleeding	–	–	5 (12.8)
Screening of osteoporosis with no active comorbidity	–	–	12 (30.8)