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EDITORIAL: THE NEW ONCOLOGIC CHALLENGES IN THE 3RD MILLENNIUM

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In the 3rd Millennium the new oncologic challenges are represented by: a) the advent of anticancer target therapy; b) elderly cancer patients; c) a new patient population, constantly growing, so called "cancer survivors"; d) virus-related tumors; and finally, e) the enormous cost to support all these aspects on cancer approach and treatment.

To better understand these "new" entities it is necessary to make some considerations on these different but "accomplices" features.

a) The end of the 2nd Millennium has been characterized by the debut, in cancer treatment, of new antiblastic drugs (AD) called target therapy. They promised new amazing anticancer-aimed effects and, at the same time, fewer toxicities than traditional AD. Really some of these new ADs respected this binomial in some cancer diseases: anticancer-aimed effects and acceptable toxicieties (e.g., trastuzumab, rituximab, erlotinib, imatinib), and many other, even maintaining their efficacy, are burdened by unexpected toxicity (e.g., cetuximab, panitumumab, sorafenib, bevacizumab, sunitinib, capatinib, crizotinib). Some new target ADs have been approved with questionably drug labeling studies, and in some cases when the therapeutic indication has been extended to other cancer diseases, the efficacy failed (e.g., erlotinib in metastatic pancreatic cancer). Appropriate and adequate information on safety, treatment response and therapy resistance are mandatory for effective and tailored cancer therapies, whereas for treatments already available, a novel clinical trial frame-work should be considered

This relates primarily to three different circumstances: existing anticancer drugs for which a more personalized label or schedule is sought (e.g., cetuximab according *KRAS* mutational status, duration of adjuvant trastuzumab), or an existing anticancer agent for another indication (e.g., imatinib in dermatofribrosarcoma). Pharmaceutical companies do not often support these studies because the low patient enrollment. The many responsibilities and obligations for the investigator/sponsor with all the related regulatory constraints often prevents the initiation of these initiatives. These problems existed frequently in the context of a better and better circumscribed and even more difficult-to-identify target population (e.g., driver mutations with a frequency of 2% to 3% in even the most widespread cancers) [1].

b) Tumors in the elderly are among the greatest emergencies of this millennium. Furthermore we can say that cancer is a disease of old age, to be faced with. In industrialized countries the population over 65 years of age is growing exponentially; epidemiological data indicate that in 2030 40% of the population will be aged over 65 years. In Europe the population over sixty increases by 1% every year. About 60% of all cancers are diagnosed in patients older than 65 years and this figure is likely to increase in coming years parallel with aging of the population. The risk of developing cancer increases by 1000 times from 40 to 80 years, and in particular, men and women above 65 years of age, have an increased risk of developing cancer 11 times higher than the popula-

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tion below that age. The increase in the average age of the population has resulted in an increased incidence of tumors in elderly patients, particularly lung cancer, head and neck, pancreatic, non-Hodgkin's lymphomas and leukemia, brain tumors, while the same trend has not arisen in cohorts of younger patients. Furthermore, the mortality rate is 15 times higher in individuals above 65 years. The advantages in the treatment of tumors obtained in the last 10 years with an overall decrease in mortality of about 6-7%, thanks to earlier diagnosis and the best available treatment, occurred in the adult population (10-20% improvement in women and men, respectively), but no advantage was obtained in the elderly, probably due to the low utilization of early diagnosis and poor therapeutic efficacy of the weapons used (when used properly) in this population [2].

c) According to the American definition of cancer survivors, we are facing two different populations of patients: many cancer survivors live with active or advanced disease, while a large and growing number of them live extended and cancer-free lives. We believe that a better definition for this patient's population could be "persons living with cancer". The number of long-term survivors is increasing according to the data published on MMWR. The number of persons in the United States ever diagnosed with cancer who were alive on January 1, 2007 has been estimated analyzing the cancer incidence and follow-up information from 9 Surveillance, Epidemiology, and End Results (SEER) programs by the US National Cancer Institute and CDC. These results demonstrated that the number of cancer survivors increased from 9.8 million in 2001 to 11.7 million in 2007, 64.8% of whom had lived ≥5 years after their diagnosis of cancer, and 59.5% of survivors were aged ≥65 years. In Italy according to the data of AIRTum (Associazione Italiana Registri Tumori), at January 1 2006, 2,243,953 persons were living with cancer; 57% (1,285,680 people, 2.2% of total population) of them could be considered as long-term survivors. Furthermore, the life expectancy of many of them ("cured") was overlapping that of the general population. Due to the increasing number of cancer survivors, medical and public health professionals must address the potential long-term and late effects of cancer on their physical and psychosocial well-being, also providing them with coordinated care, and promoting healthy behaviors such as smoking cessation and physical activity, to reduce the risk of new o recurrent cancer and increase programs for early detection of new or recurrent cancers [3,4].

d) The advent of highly active antiretroviral therapy (HAART) has dramatically extended the survival rates of patients with human immunodeficiency virus (HIV), leading to suppression even though not to eradication of HIV. In HIV-infected patients, cancer has become a growing problem representing the first cause of death. HIV has been linked to malignancies since the beginning of its history, in 1981, when Kaposi's sarcoma was reported for the first time. Subsequently, two other malignancies have been related to HIV, being classified as AIDS-defining cancers (ADCs): non-Hodgkin's lymphoma (NHL) and invasive cervical cancer. In addition, a large number or worldwide studies have shown that HIV infection raises the risk of many non-AIDS-defining cancers (NADCs), including carcinoma of the anus, testis, lung, colon, skin (basal cell skin carcinoma and melanoma), Hodgkin's disease and hepatocellular carcinoma (HCC). It is well established that the incidence of ADCs has declined in the HAART era; NADCs, on the contrary, have gradually emerged. Zucchetto et al [5] evaluated the mortality for NADCs among 10392 Italian patients with AIDS, who were diagnosed between 1999 and 2006, compared with the general population of the same age and sex. NADCs were accounted as the underlying cause of death for 7.4% of HIV-infected. The authors found a 6.6-fold elevated risk of death for NADCs among persons with AIDS, especially due to cancers with viral etiologies: significantly elevated standardized mortality rates (SMRs) were, in fact, recorded for anal cancer, a human papilloma virus-associated tumor (SMR 270), Hodgkin's lymphoma, associated with Epstein Barr virus (SMR 174) and HCC, associated with chronic hepatitis B and C virus infections (SMR 11.1). Despite these evidences, to date many HIV-positive patients are undertreated due to only medical discriminatory attitude. Many studies have demonstrated that if the therapeutic approach is multidisciplinary and performed at highly specialized Centers the results in terms of response to treatment, toxicities and overall survival are comparable with those of the general population [6-18].

e) Recent models in cancer therapy are based primarily on validated multitrials approach, that includes, often, the newer patented drugs. However, global current concept of governative healthcare systems stimulate that the new medical care must be delivered at equal or lower

cost with better patient outcomes. Furthermore, trials evaluating the precise economic impact of various cancer treatments are still low. In general, there are three main types of economic analysis for cancer therapy that differ primarily in the evaluation of health outcome: cost-effectiveness, cost-utility and cost-benefit parameters. The primary aim of a cost–effectiveness analysis is to provide sufficiently robust information for decision-makers to allocate resources to healthcare interventions. Recently, several methods to assess the quality of cost-effectiveness, cost-utility and cost-benefit in the cancer managements have become available. A relevant example is the National Institute for Health and Clinical Excellence (NICE). NICE forms a diverse clinical Advisory committee, which stimulates Pharma and Academic communities to produce a robust set of data, including the design and data source, for economic models of personalized healthcare. Personalized medicine includes genomic tests of each patients and their disease into their clinical treatments, so as minimize toxicity and maximize benefits due to specific tailored treatments. It is well known that Pharmacogenomics tests, performed before drug treatment, lower overall medical costs and provide higher quality of life and longer life expectancy [19]. NICE, also providing a method to measuring Quality-Adjusted Life-Years (QUALYs); metrics that combine heterogenic information on outcomes, analytical, and cost-effectiveness for each treatment.

The future implementation of the methods for measuring the QUALYs will lead to personalized treatment and eventually will shift the balance from disease relapse toward disease eradication.

We believe that the right way to face these challenges is based on a multidisciplinary treatment approach and to rationalize the costs of these treatments due to aimed-interventions.

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