

Editorial – A tailored approach in geriatric oncology: turning a problem into an opportunity for the elderly

F. FIORICA¹, M. GABBANI¹, M. ZANINELLI², M. MURARO¹, P. PINTON³, C. GIORGI³

¹Department of Radiation Oncology and Nuclear Medicine, AULSS 9 Scaligera, Verona, Italy

²Department of Medical Oncology, AULSS 9 Scaligera, Verona, Italy

³Department of Morphology, Surgery and Experimental Medicine, Section of Pathology, Oncology and Experimental Biology, Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy

The “silver tsunami”¹, the clinical scenario with the increase of elderly cancer patients, is becoming, year after year, more and more concrete. Even more, it is shaping up to be a perfect storm in cancer treatment decisions. On the one hand, the escalation in the incidence of cancer diagnoses in elderly population setting leading to the raised incidence linked to the increase in life expectancy (indeed cancer is defined today as a chronic degenerative disease²). On the other hand, a “conscious ignorance” in geriatric oncology. The “Achilles’ heel” of approach based on evidence-based medicine (EBM) is represented by the availability of this same evidence. Socket suggested the use of “the best external evidence”³ to guide clinical decisions. Unfortunately, elderly cancer patients are under-represented in clinical trials, especially the older (age range 75-84) and the oldest patients (>85). As undelighted by Cartabellotta⁴, the absence of evidence can lead to decision-making paralysis because EBM does not require clinical decisions to be based on “best possible evidence”. This is probably the reason why a nihilistic approach classically winds among oncologists to treat elderly patients. Furthermore, to complicate this picture, the heterogeneity of this population is crucial, in fact it is simple either to find subjects very fit and subjects very frail enough not to be able to live independently. Obviously, these different scenarios play a decisive role in treatment results as efficacy and tolerance. All this overview helps us to understand why treating elderly cancer is still very tricky. We have demonstrated that there is a strong correlation between the comorbidities (reducing the functional organ reserve of the patient) and the possibility to have a beneficial effect by the oncological treatments bearing their toxicities⁵. It is possible to deliver radiotherapy to a fit elderly patient safely and effectively for prostate cancer⁶, for breast cancer⁷, for NSCLC⁸ and in other types of tumours. Some other elderly patients can benefit from chemotherapy with oxaliplatin⁹. It is not surprising that elderly gastrointestinal cancer patients tolerate a toxic chemotherapy regimen such as FOLFOX10 or XELOX1^{11,12}.

As you can see, all evidence comes from retrospective or prospective studies, so it is extremely hard to apply it.

The American Geriatrics Society recently encourages active recruitment of older adults, adds standard measures of function and/or frailty, and changes review criteria to ensure the health status of a study population mirrors typical clinical populations¹³.

While we expect data from new RCTs, we have a great opportunity to modify the treatment cancer idea and therefore to personalize really the same treatment for each individual patient, trying to do “the right thing to the right person”.

The first step for this personalization process is obviously determining the biological age of the patient. Indeed, it is essential to treat patients according to their organ reserve. The patient should be treated in the best possible ways recalling the motto “primum non nocere”.

The second step is not to consider malignant tumour cell as the only focus for the treatment. Even today, the oncologists of different branches (chemotherapy, radiotherapy, and surgery) have a cancer centric view, so they use surgery, target therapy, chemotherapy and/or radiotherapy to kill tumour

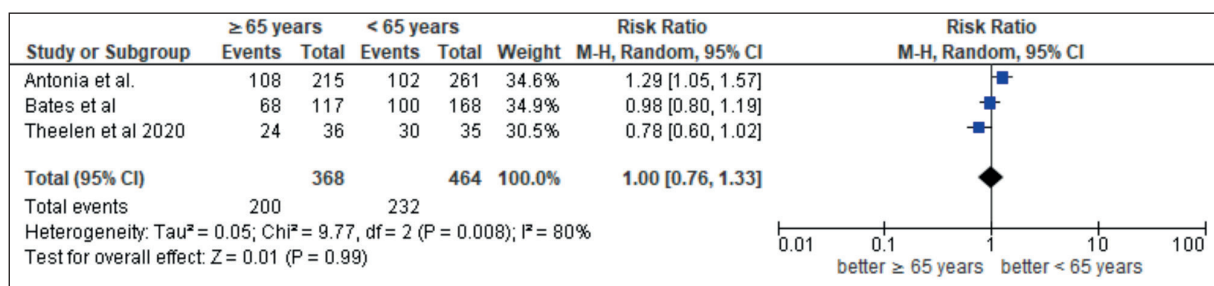


Figure 1. 1-year overall survival. Meta-analysis of 3 studies of ICI-RT association reporting effect size for patients ≥ 65 years and for patients < 65 years. The risk ratio (RR) and 95% confidence interval (CI) for the effect of treatment on 1-year overall survival are shown on a logarithmic scale. The studies are criteria arranged in the meta-analysis by Fiorica et al¹⁶.

cells. It is demonstrable that in tumour mass the stromal cells represent the majority of cell types. A focus only on malignant tumour cells has been deemed inaccurate. It is necessary a global vision considering tumour mass with endothelial cells, fibroblasts, macrophages, neutrophils, dendritic cells, and cytotoxic T cells.

Since there is not a real EBM approach in geriatric oncology, this time can be the beginning of a cultural revolution that leads to review knowledge and thinking about cancer globally. Softly, this revolution is started introducing immune checkpoints inhibitors in clinical practice. Let's begin, for example, with radiation oncology which is now losing the connotation of "tumour" sniper" and gaining the role of modulatory tool that facilitates the recruitment and activation of the immune system to fight tumours¹⁴.

The immune system of the elderly is different from that of a younger person. In the latter, it is more normal to find a hyperergic immune system differently than in the elderly. Therefore, it is reasonable to think that there are two macro-scenarios of tumour-host interaction: the first one is the most active immune system and the second one is the laziest immune system. Between the two extremes, there are obviously intermediate and remarkably heterogeneous situations. In our opinion, only by understanding which interaction takes place in the subject, one can optimize the therapeutic approach and reach to a real customization of the treatment.

A person with a lazy immune system must be stimulated to induce an immune cell mediated response. Normally the elder has a lazy immune system to arouse.

A recent study¹⁵, analysing 24 eligible randomised trials (including a total of 8157 younger and 6104 older cancer patients) highlighted that the survival benefit conferred by ICI was not age-dependent. In this context, it is necessary to make the most of the interactions of ICI with another oncological arm, for example with radiation therapy, which can act on several levels of this interaction. In our recent study, analysing the effect of the association of immune check point inhibitors and radiotherapy in non-small cell lung cancer, we concluded that combination increase the overall survival¹⁶. If we analysed these data combining the effect for patients with age $<$ or ≥ 65 years, there is no difference in OS between these two groups: 54.3% of 368 included patients with age ≥ 65 years and 50% of 464 with age < 65 years live at 1 year with a RR 1 (95% CI 0.76-1.33; $p = 0.99$) (Figure 1). It is really a great opportunity to use all pragmatic evidence to increase the efficacy and effectiveness of immunological arms and to adjust the host microenvironment, where tumour growths, towards an anti-neoplastic response.

Age does not usually restrict the active treatment of cancer, but the patient's other diseases and poor general condition do. Geriatric and psychosocial assessment of the patient's situation help in making the treatment decisions. Close collaboration with other health professionals will be a tool providing adequate therapy to elderly patients with cancer in order to increase treatments' effectiveness and to decrease cost¹⁷. There are promising achievements in each of the requirements listed, but a huge, holistic effort has still to be made.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) Roehr B. US geriatric mental health workforce needs to expand, says Institute of Medicine. *BMJ* 2012; 345: e4686.
- 2) Rew DA. Cancer--a degenerative disorder? *Eur J Surg Oncol* 1998; 24: 362-366.
- 3) Sackett DL, Rosenberg WMC, Gray JAM, Haynes BR, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71.
- 4) Cartabellotta A. Evidence-based medicine: criticisms and future challenges. *Recenti Prog Med* 2006; 97: 640-646.
- 5) Fiorica F, Zanghi A, Pascale G, Nuta O, Del Pup L, Stefanelli A, Cartei F. Is effective and safe a radiochemotherapy approach in elderly cancer patients? A review. *Anticancer Agents Med Chem* 2013; 13: 1430-1437.
- 6) Fiorica F, Berretta M, Colosimo C, Berretta S, Ristagno M, Palmucci T, Palmucci S, Lleshi A, Ursino S, Fisichella R, Spartà D, Stefanelli A, Cappellani A, Tirelli U, Cartei F. Safety and efficacy of radiotherapy treatment in elderly patients with localized prostate cancer: a retrospective analysis. *Arch Gerontol Geriatr* 2010; 51: 277-282.
- 7) Fiorica F, Berretta M, Ursino S, Fisichella R, Lleshi A, Fiorica G, Stefanelli A, Zini G, Tirelli U, Zanghi A, Cappellani A, Berretta S, Cartei F. Adjuvant radiotherapy on older and oldest breast cancer patients after conservative surgery: a retrospective analysis. *Arch Gerontol Geriatr* 2012; 55: 283-288.
- 8) Fiorica F, Cartei F, Ursino S, Stefanelli A, Zagatti Y, Berretta S, Figura S, Maugeri D, Zanet E, Spartà D, La Morella C, Tirelli U, Berretta M. Safety and feasibility of radiotherapy treatment in elderly non-small-cell lung cancer (NSCLC) patients. *Arch Gerontol Geriatr* 2010; 50: 185-191.
- 9) Berretta M, Zanet E, Nasti G, Lleshi A, Frustaci S, Fiorica F, Bearz A, Talamini R, Lestuzzi C, Lazzarini R, Fisichella R, Cannizzaro R, Iaffaioli RV, Berretta S, Tirelli U. Oxaliplatin-based chemotherapy in the treatment of elderly patients with metastatic colorectal cancer (CRC). *Arch Gerontol Geriatr* 2012; 55: 271-275.
- 10) Berretta M, Cappellani A, Fiorica F, Nasti G, Frustaci S, Fisichella R, Bearz A, Talamini R, Lleshi A, Tambaro R, Cociolo A, Ristagno M, Bolognese A, Basile F, Meneguzzo N, Berretta S, Tirelli U. FOLFOX4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study. *Arch Gerontol Geriatr* 2011; 52: 89-93.
- 11) Berretta M, Aprile G, Nasti G, Urbani M, Bearz A, Lutrino S, Foltran L, Ferrari L, Talamini R, Fiorica F, Lleshi A, Canzonieri V, Lestuzzi C, Borsatti E., Fisichella R., Tirelli U. Oxaliplatin and capecitabine (XELOX) based chemotherapy in the treatment of metastatic colorectal cancer: the right choice in elderly patients. *Anticancer Agents Med Chem* 2013; 13: 1344-1353.
- 12) Berretta M, Nasti G, De Divitiis C, Fisichella R, Spartà D, Baresic T, Ruffo R, Urbani M, Tirelli U. Safety and efficacy of oxaliplatin-based chemotherapy in the first line treatment of elderly patients affected by metastatic colorectal cancer. *WCRJ* 2014; 1: e235.
- 13) Vaughan CP, Dale W, Allore HG, Binder EF, Boyd CM, Bynum JPW, Gurwitz JH, Lundebjerg NE, Trucil DE, Supiano MA, Colón-Emeric C. AGS Report on Engagement Related to the NIH Inclusion Across the Lifespan Policy. *J Am Geriatr Soc* 2019; 67: 211-217.
- 14) Menon H, Ramapriyan R, Cushman TR, Verma V, Kim HH, Schoenhals JE, Atalar C, Selek U, Chun SG, Chang JY, Barsoumian HB, Nguyen Q-N, Altan M, Cortez MA, Hahn SM, Welsh JW. Role of Radiation Therapy in Modulation of the Tumor Stroma and Microenvironment. *Front Immunol* 2019; 10: 193.
- 15) Ninomiya K, Oze I, Kato Y, Kubo T, Ichihara E, Rai K, Ohashi K, Kozuki T, Tabata M, Maeda Y, Kiura K, Hotta K. Influence of age on the efficacy of immune checkpoint inhibitors in advanced cancers: a systematic review and meta-analysis. *Acta Oncol Taylor & Francis*; 2020; 59: 249-256.
- 16) Fiorica F, Tebano U, Gabbanì M, Perrone M, Missiroli S, Berretta M, Giuliani J, Bonetti A, Remo A, Pigozzi E, Tontini A, Napoli G, Luca N, Grigolato D, Pinton P, Giorgi C. Beyond Abscopal Effect: A Meta-Analysis of Immune Checkpoint Inhibitors and Radiotherapy in Advanced Non-Small Cell Lung Cancer. *Cancers (Basel)* 2021; 13: 2352.
- 17) Di Francia R, De Lucia V, Giordano A, Benincasa G, Mignano M, Berretta M. Pharmacogenomics as a tool to prevent drug-related hospitalization of elderly cardiology-oncology patients receiving chemotherapeutic agents and multiple symptomatic treatments: a pilot study planned for the Italian health system. *Eur Rev Med Pharmacol Sci* 2019; 23: 8695-8701.