

Old myths about old patients: the case of non-small cell lung cancer

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Comment on: Gajra A, Zemla TJ, Jatoi A, *et al.* Time-to-Treatment-Failure and Related Outcomes Among 1000+ Advanced Non-Small Cell Lung Cancer Patients: Comparisons Between Older Versus Younger Patients (Alliance A151711). J Thorac Oncol 2018;13:996-1003.

Submitted Aug 22, 2018. Accepted for publication Sep 05, 2018. doi: 10.21037/tlcr.2018.09.24 View this article at: http://dx.doi.org/10.21037/tlcr.2018.09.24

Demographics of the cancer patients are shifting where an increase of the proportion of elderly patients is observed because the increase of the life expectancy and better outcomes obtained with new systemic treatments (1).

Aging is associated with a set of physiological changes, including decreased stem cell reserves with a subsequent deficiency in tissue repair and decline in organ function increasing the risk of toxicity due to chemotherapeutic agents (2). The treatment of a geriatric patient with cancer in the clinical routine is challenging because some particular characteristics of this age group such as the frailty, comorbid conditions, polypharmacy and underrepresentation in clinical trials, while in the other hand, this group is less likely to receive intensive but beneficial cancer treatments (3-5).

In a pooled analysis of 1,006 advanced non-small cell lung cancer (NSCLC) patients enrolled in three firstline CALGB clinical trials and published in the *Journal* of *Thoracic Oncology*, Gajra *et al.* [2018] demonstrated a comparable time-to-treatment failure (TTF) between older and younger patients (2.9 vs. 3 months, respectively) where none statistical differences were found after adjustment by performance status or chemotherapy by trial (6).

In this study TTF was defined as chemotherapy discontinuation prior to completion of the planned 6 cycles for any reason. Despite these similarities, there were significant differences in reasons for early chemotherapy cessation (P=0.004). Chemotherapeutic agents used in these trials were paclitaxel, carboplatin plus paclitaxel, carboplatin and gemcitabine with or without zileuton or celecoxib, carboplatin plus pemetrexed and carboplatin plus gemcitabine (6).

Death by treatment-associated toxicity is an undesired event in older patients; however, since more than two decades ago, several studies demonstrated that an old age is not a reason to restrict the systemic treatment. Gómez *et al.* [1998], evaluating a cohort of patients aged ≥ 60 years old with intermediate or high-grade NHL treated with CHOP chemotherapy, determined that the performance status and not the age are related to the risk of death by chemotherapy toxicity (7). In the same way, efficacy of CHOP treatment in the group of patients aged 61–69 years and ≥ 70 years was similar but significant differences in toxicities were observed (8).

Inaccurate expectation about the toxicity and tolerance of treatments in older patients with cancer could lead to less aggressive or substandard therapy reducing the benefit of these therapies. The avoidance of adjuvant chemotherapy in older patients was associated with worse outcomes in colorectal cancer. In the QUASAR trial that enrolled 3,239 patients and compared adjuvant chemotherapy *vs.* observation, patients with adjuvant chemotherapy had a lower risk of recurrence (HR =0.78; 95% CI: 0.67–0.91; P=0.001) and lower risk of death (HR =0.82; 95% CI: 0.70–0.95; P=0.008) (9).

In lung cancer, the landscape for elderly patients is similar than observed in other malignancies, where several

Translational Lung Cancer Research, Vol 7, Suppl 4 December 2018

patients do not receive chemotherapy in the metastatic setting, only 66% of patients with locally advanced NSCLC receive any treatment and where the 45% of these patients receive standard combined treatments with chemotherapy and radiotherapy (1).

In the recent report by Gajra *et al.* [2018], patients aged ≥ 65 years and < 65 shared similar rates of chemotherapy toxicity and death as reasons for stopping chemotherapy while there were differences in stopping chemotherapy by patient choice (15% *vs.* 6%) and cancer progression (41% *vs.* 55%), respectively (6). These results highlight the need for more research in this age group and the urgent need to improve the adequate selection of older patients who are able to receive complete doses of chemotherapy or radiotherapy.

Many questions will be answered with the results of the NVALT25-ELDAPT trial combining an observational and randomized controlled design evaluating the appropriateness of treatments in stage III NSCLC \geq 75 years old patients. This trial is currently recruiting participants. Patients are screened with an extensive geriatric assessment and classified as fit or frail. Patients classified as fit are randomized to receive concurrent or sequential chemo-radiation while patients unsuitable for sequential chemo-radiation are treated according to oncologist's decision (10).

In the age of new therapies that are improving long-term outcomes, such as precision therapy and immunotherapy, we have to ban old myths about cancer treatment to improve the outcomes of our older patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Cite this article as: Pinto JA, Raez LE. Old myths about old patients: the case of non-small cell lung cancer. Transl Lung Cancer Res 2018;7(Suppl 4):S362-S363. doi: 10.21037/tlcr.2018.09.24

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