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Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: A literature review

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ABSTRACT

Purpose: Aim of the present review is to assess present data about the use of the association of Radiotherapy (RT) and targeted therapy/immunotherapy (TT/IT) in elderly people.
Design: PubMed database was searched for English literature published up to December 2017 using the keywords "radiotherapy" combined with "bevacizumab", "cetuximab", "trastuzumab", "erlotinib", "gefitinib", "sorafenib", "sunitinib", "vismodegib", "sonidegib", "ipilimumab", "pembrolizumab", "nivolumab". Studies performing RT and TT/IT in people aged > 65-years were evaluated focusing on safety, toxicity and efficacy. Studies eligible for inclusion were: case reports, retrospective/prospective studies in which RT and new drugs were used concomitantly or sequentially, focusing on elderly sub-group.
Results: The systematic search identified 626 records. After exclusion of duplicates, full-text review, cross-referencing and paper that did not respect the inclusion criteria, 81 studies were included in this review. In elderly patients the combination of RT with cetuximab or bevacizumab seems feasible but with higher reported side effects. Patients' age should not limit the association of trastuzumab and RT in HER2 positive breast cancer. The concurrent administration of TKIs and RT appears to be feasible and effective. Regarding the Immune Check Point inhibitors and RT, tolerance seems similar among older and younger people but definitive data are lacking. Instead, the association of RT and vismodegib/sonidegib remains investigational.
Conclusion: TT/IT in association of RT seems to be safe, but in elderly patients data concerning safety and toxicity are limited. Specific clinical trials on this population are encouraged.

1. Introduction

Cancer is primarily a disease of elderly people, around 50% of all new cancer cases each year are diagnosed in people over 70, with an increasing mortality rate with age (Cancer Research UK, 2018a,b). Moreover, owing to the increase in life expectancy, the number of elderly people is projected to increase more than 60% in the following 15-years. Therefore in the next future the age of cancer population will continue to grow and elderly people will represent 70% of new cancer diagnoses/year (Cancer Research UK, 2018b; He et al., 2015; Yanvik and Ries, 2004).

The proper therapeutic approach for elderly cancer patient is still controversial. Elderly are often underrepresented in clinical trials and, those included, do not represent the whole elderly population as they are extremely selected. Moreover the presence of comorbidities, which decrease the organ functional reserve, make the decision for

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therapeutic approach more difficult.

Radiotherapy (RT), together with surgery and chemotherapy (CT), is one of the primary modalities proposed and utilized in more than 60% of cancer patients, showing a benefit in terms of local control and overall survival (OS) (Delaney et al., 2005; Hanna et al., 2018). In the last years, the introduction of targeted-therapies (TT) and immunotherapy (IT) has changed the landscape of cancer treatment. Unfortunately, for elderly patients few data are available in literature about safety/efficacy of TT/IT alone and in association of RT. Recognizing the urgent need for more and stronger research on the treatment approach of geriatric cancer patients, the oncological communities are working to answer this need.

Daste et al. (2016) reviewed the use of targeted therapies in elderly and underlined that specific adverse events could have no consequences for young people but might be significant in elderly patients. He concluded that, although the majority of TTs can be prescribed in the elderly, strict monitoring is necessary especially in the case of numerous comorbidities because in elderly people each disease can affect another one (Daste et al., 2016). The same group reviewed also data of IT in elderly and conclude that, even though further prospective studies are warranted, tolerance between younger and older groups was similar and better than for cytotoxic treatment (Daste et al., 2017).

All data reported in the above mentioned reviews do not take in account the role of RT, even though its use is widespread among elderly patients both with a curative or palliative intent.

Thus, aim of the present review is to assess the published data about the use of the association of RT and new drugs (TT/IT) in elderly people.

2. Material and methods

PubMed database was searched for English literature published up to December 2017 using the keywords “radiotherapy” combined with “bevacizumab”, “cetuximab”, “trastuzumab”, “erlotinib”, “gefitinib”, “sorafenib”, “sunitinib”, Hedgehog signaling pathway inhibitor, Ipilimumab, Nivolumab and Pembrolizumab. Studies performing RT and TT/IT in patients over 65-years were evaluated focusing on safety, toxicity and efficacy. The cut off of 65 years was chosen to evaluate all spectrum of elderly patient, according to Balducci classification that identify three categories: 1-young old patients (65–75 years of age); 2-old patients (76–85 years) and 3- oldest old patients (older years 85 years) (Balducci et al., 2004).

Studies eligible for inclusion in this review were: case report, retrospective or prospective studies in which RT and new drugs were used concomitantly or sequentially; studies in which the evaluation of an elderly sub-group was reported. For each drug, 2 reviewers used these criteria to independently select the eligible studies. Exclusion criteria were: study without any specific results, abstracts or poster presentations.

3. Results

The systematic search identified 626 records from PubMed. After exclusion of duplicates, full-text review, cross-referencing and papers that did not respect the inclusion criteria, 81 studies were included in this review (Fig. 1). Table 1 shows studies with largest sample size (> 15 patients).

3.1. Bevacizumab

Bevacizumab is a humanized monoclonal antibody that binds and neutralizes vascular endothelial growth factor A/VEGF-A.

3.1.1. Brain tumor

A phase-II trial evaluated the addition of concomitant and adjuvant Bevacizumab to RT (60 Gy/30fractions) and temozolomide (TMZ) for the treatment of glioblastoma (Lai et al., 2011; Saran et al., 2016). Median age was 57.4 years with a range up to 76. Younger patients had worse survival, while no difference was observed between patients over 50 and historical control (median OS: 19.6 months). Additional toxicity was observed in the bevacizumab group, without relationship with age. Babu et al. (2016) published a retrospective analysis of 120 elderly patients with glioblastoma treated +/- adjuvant bevacizumab. Despite the absence of toxicity data, bevacizumab seemed to improve OS (20.1 vs 7.9 months; $p < 0.0001$).

3.1.2. Head and neck cancer (HN)

Data regarding the association of Bevacizumab and RT in HN elderly population are scarce, pointing nonetheless to an increasing risk of toxicity (Seiwert et al., 2008; Salama et al., 2011).

3.1.3. Rectal cancer (RC)

Phase-I/II trials investigated the role of Bevacizumab in association with standard chemoradiation (Willett et al., 2010; Kennecke et al., 2011), without clear findings for elderly patients. Velenik et al. (Velenik et al., 2011) investigated the role of neoadjuvant bevacizumab plus capecitabine and RT in 61 patients (median age 60 years, range: 31–80) with locally advanced RC (LARC). Pathologic complete response (pCR) was observed in 13.3% of patients but surgical complications were frequently reported. Toxicity in patients categorized according to age was not evaluated. Another phase-II trial enrolled 42 LARC patients to receive bevacizumab followed by RT plus bevacizumab, capecitabine, and oxaliplatin. Patients up to 84 years were included. Bleeding episodes (17%) and surgical complications, including pelvic infection (14.3%), delayed healing (7.1%) and anastomotic leak (4.8%) were observed (Kennecke et al., 2011).

3.1.4. Highlights

- *RT and bevacizumab for brain tumors increases the incidence of toxicity with a possible benefit in outcomes.*
- *Bevacizumab in combination with RT in HN and rectal cancer increase the rates of complications.*

3.2. Trastuzumab

Trastuzumab is a humanized recombinant monoclonal antibody binding the extracellular domain of HER2 receptor (Figueroa-Magalhães et al., 2014).

3.2.1. Breast cancer (BC)

An extensive review of anti-HER2 agents administered concomitantly with RT has been published (Mignot et al., 2017). The authors gathered the experiences from approximately 1600 patients, showing a limited incidence of cardiac toxicity related to concomitant use of trastuzumab and whole breast RT. Mean age of patients' population across studies was below 50 years, with a proportion of patients over 65 inferior to 10%. De Santis MC et al (De Santis et al., 2017) published the results about the feasibility of concomitant use of trastuzumab and adjuvant hypofractionated-RT (42.4 Gy/16fractions) in an elderly population (De Santis et al., 2017). CT was utilized in 170 patients and 30% of them received trastuzumab. Trastuzumab patients were at higher risk of cardiac toxicity ≥ G1 (odds ratio, 4.3; $P = 0.01$), and at lower risk of acute skin toxicity ≥ G2 (odds ratio, 0.4; $P = 0.03$) than CT alone patients.

3.2.2. Esophageal cancer

A Phase-I/II trial evaluated the potential benefit of adding trastuzumab to concurrent chemo-RT (Safran et al., 2007). Nineteen patients affected by adenocarcinoma of the esophagus were enrolled, 50% of the entire population was elderly. 2-year survival was 50%, and toxicity was not age-related (only one G4 and one G3 esophagitis).

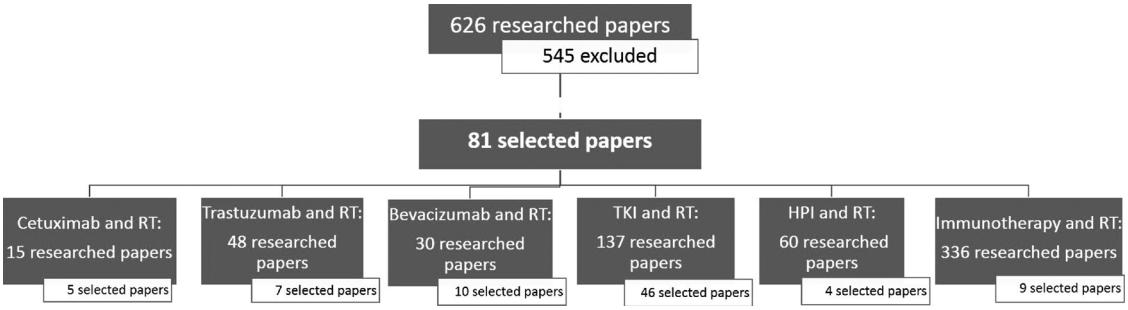

Fig. 1. Modified PRISMA flowchart.

3.2.3. Bladder cancer

The RTOG 0524 study included 20 patients receiving RT plus paclitaxel and trastuzumab (group 1) or RT plus paclitaxel alone (group 2, 48 patients). Median age was 79.5 (range 51–86) and 73 (range 55–90) in group 1 and 2, respectively. In Group 1, 40% of patients discontinued the planned therapy due to side effects; 35% of patients presented acute treatment-related adverse events (including one gastrointestinal G5 case) (Michaelson et al., 2017).

3.2.4. Highlights

- *Trastuzumab in combination with breast RT does not increase cardiac toxicity.*
- *Trastuzumab in association with RT for gastric or bladder cancer is investigational.*

3.3. Cetuximab

Cetuximab is an epidermal growth factor receptor [EGFR] inhibitor.

3.3.1. HN cancer

Cetuximab is so far the only targeted agent to clearly show a benefit in terms of OS in patients with locoregionally advanced and recurrent/metastatic squamous cell HN carcinoma (SCCHN) (Bonner et al., 2006; Vermorken et al., 2008). The Bonner trial randomized 424 patients (26% were elderly) to receive cetuximab plus RT or RT alone. OS benefit of cetuximab was proven only in patients under 65, with comparable toxicity. Conversely, real-world experiences showed higher side effects and lower efficacy (Giro et al., 2009; Magrini et al., 2016; Specenier and Vermorken, 2016). Limited experiences have been published focusing on the association of RT/cetuximab in an elderly SCCHN population, which reported an increased risk of side effect, leading to discontinuation of cetuximab (Falk et al., 2017; Jensen et al., 2010).

Two prospective phase-II trials evaluated the combination of stereotactic body radiotherapy (SBRT) and cetuximab (Lartigau et al., 2013; Vargo et al., 2015). Median age was 60 and 63 years, respectively. Reported severe toxicities were reasonably low and not age-related.

3.3.2. Rectal cancer

Published experiences involved around 500 patients with a median age of 60 years, but the exact proportion of elderly patients has not been specified. Overall G3/G4 gastrointestinal toxicity was 16.6%, not age-related across the reported experiences, without a clear benefit on pCR by the addition of cetuximab to standard radio-CT (Glynne-Jones et al., 2013).

3.3.3. Highlights

- *Cetuximab in combination with RT in SCCHN is still controversial with higher reported skin toxicities*
- *Cetuximab plus RT in rectal cancer is investigational*

3.4. Erlotinib/Gefitinib

Erlotinib and Gefitinib, small molecules tyrosine kinase inhibitors (TKIs), are potential radiosensitizers (Tanaka et al., 2006; Chinnaiyan et al., 2005).

3.4.1. Non-small-cell lung cancer (NSCLC)

Several data showed feasibility/efficacy of TKIs alone treatment in elderly patients (Roviello et al., 2018; Daste et al., 2016), while no definitive results are present on the association with RT in this population.

A Chinese study evaluated 122 elderly patients with localized NSCLC treated with gefitinib combined with SBRT Pan et al., 2013. The patients were divided into 3 groups: Group A (gefitinib + SBRT, 35 patients), group B (SBRT alone, 45 patients) and group C (gefitinib alone, 42 patients). The results showed better outcomes for the combined treatment, in terms of PFS and OS, feasibility and toxicity (G3 skin rash and diarrhea).

Ready et al. (2010) evaluated the addition of gefitinib to RT in 68 patients with unresectable stage III NSCLC, dividing them in a 21 poor-risk stratum (PS 2 and/or 5% weight loss in previous 3 months) and a good-risk stratum (PS 0–1, 5% weight loss). Median age was 68 years: patients over 70 were 33% in poor-risk and 21% in good-risk group Ready et al., 2010. All patients received two cycles of paclitaxel/carboplatin and sequential RT (66 Gy) with concomitant gefitinib. The good-risk group received also concomitant CT. In the poor-risk group, the addition of gefitinib did not increase in-field high-grade acute toxicity, no correlation with age was found. Even though results were promising in poor-risk stratum, disappointing results in good-risk patients led to a premature closure of this study (Ready et al., 2010). Conversely, other authors reported conflicting results (Lau et al., 1998; Davies et al., 1998; Komaki et al., 2015).

In the CALGB 30605/RTOG 0972 trial, 75 patients with poor-risk (PS 2 or PS 0–1 and ≥10% weight loss within 3 months prior to enrollment) and unresectable stage-III NSCLC were treated with induction CT followed by RT and concurrent erlotinib (Lilenbaum et al., 2015; Kelly et al., 2008) : 73% of patients were over 65 years. Despite the poor-risk and the advanced age of the population, treatment was well tolerated; compliance to protocol was 80% with only 5% of interruptions for adverse events. Median PFS and OS were 11 and 17 months, respectively; reported 1-year OS was 57%. Overall, the frequency of G3-4 neutropenia, G3 anemia and G3 esophagitis were 10%, 10% and 5%, respectively. Diarrhea and skin rash G3 toxicities were observed in 9% and 4% of patients, respectively.

Martinez e et al. (Martinez et al., 2016) published a multicenter randomized controlled phase-II trial in elderly patients treated with erlotinib in combination with RT (60 patients) versus RT alone (30 patients), without significant differences in terms of outcomes (Martinez et al., 2016). Furthermore, the number of patients with adverse events ≥ G3 was significantly higher in the combined arm (65%) compared to RT alone (37.9%), even if side effects were largely manageable.

Table 1
Main studies on elderly population.

Drug	Author-year	Trial	N° pts	Age Median (range)	Tumour site	Treatment	RT dose	Toxicity	Efficacy
Bevacizumab	Babu R[9]/2016	Retrospective	120	71 (65-89)	glioblastoma	Adjuvant RT + tmz+/- bevacizumab	60 Gy/30 fx	Not reported	OS improvement ($p < 0.0001$) in arm with Bevacizumab
Trastuzumab	De santis MC[17] /2017	Prospective	51/710	> 65 yy	Breast cancer	Adjuvant hypofractionated RT + CT +/- Trastuzumab	42.4 Gy /16 fx	↑ G1 cardiac tox and ↓ ≥G2 skin tox	/
Cetuximab	Falk AT[25]/2017	Retrospective	35	74 (70-86)	SCCHN	RT + Cetuximab	66-70 Gy/33-35 fx	G3 radioepithelitis: 62.4% Mucositis:31.4%	2-year local-regional relapse and metastatic relapse-free survivals were 59% and 74%, respectively
Cetuximab	Jensen AD[26]/ 2010	Retrospective	73	69	Primary/recurrent SCCHN	RT + Cetuximab	−66 Gy for definitive RT −45 Gy for re-RT	- allergic reaction 5.6% - Skin reactions leading to cetuximab breaks 1,4% -Skin reactions leading to discontinuation of cetuximab 4,2%	Overall response rate was 59,4%, median LR, PFS and OS were 18, 15 and 18 months, respectively
Gefitinib	Pan D[34]/ 2013	Retrospective	112	74.5 (70-83)	NSCLC stage II-III	SBRT + gefitinib vs SBRT alone vs gefitinib alone	36-48 Gy/4-6.5 Gy per fraction	- Skin rash 6% - diarrhea 9%	Better PFS and OS in SBRT + gefitinib group (7.8 vs. 5.9 vs. 5.1 months and 15.5 vs. 9.6 vs. 10.3 months)
Erlotinib	Martinez[41]/2016	Phase II	90	79.2 (76.7-81.7)	Locally advanced NSCLC	RT vs RT + Erlotinib	66 Gy / 33 fx	G3 toxicity higher in combined arm	No difference in OS (15.3 versus 12.9 months) and PFS (11.4 vs. 8.9 months). Cutaneous rash was associated with a significant longer PFS (11.1 vs 2.8 months, respectively)
Gefitinib	Xu Y[45]/2015	Phase II	20	76	Esophageal SCC	RT + Gefitinib	50.4 Gy/28 fx	−20% G3 esophagitis −5% G3 pneumonitis	Median OS: 14 months Median PFS: 7 months
Erlotinib	Iyer R[46]/2013	Prospective	17	78	Esophageal SCC	RT + Erlotinib	50.4 Gy/28 fx	29% G3-4 toxicity	Median OS and PFS:7.3-4.5 months Better OS and PFS in EGFR amplified tumours
Erlotinib	Zhai Y[47]/2013	Prospective	18	71.5	Esophageal SCC	RT + Erlotinib	60 Gy/30 fx	G3 esophagitis 27.8% G3 skin rash: 11.1%	The median time of OS and PFS was 21.1 and 12 months 2 yy OS, PFS and LRRFS progression-free survival were 44.4%, 38.9%, and 66.7%, respectively.
Erlotinib	Zhang ZB[48]/ 2012	Phase II	33	> 70	Esophageal SCC	RT + Erlotinib	60 Gy/30 fx	No G3-4 toxicity	1-2 yy OS: 66.3%- 49.7%
Erlotinib	Song T[49]/2017	Retrospective	68	74 (70-91)	Esophageal SCC	RT + Erlotinib vs CRT (paclitaxel plus cisplatin)	60 Gy/30 fx	More treatment-related toxicities in CRT group than RT + erlotinib	1-yy, 3-yy OS were 75.0% vs 78.0%, 42.7% versus 36.8% for CRT or RT + erlotinib ($P = .979$)
Sorafenib	Wada Y[63]/ 2017	Retrospective	62	> 60	mHCC	RT + Sorafenib vs Sorafenib alone	50 Gy/25 fx (median)	Thrombocytopenia, leukopenia, and skin reaction higher in combined group	PFS (13.5 and 31.2 months) and OS (3.3 and 12.1 months, $p < 0.01$) higher in combined group vs Sorafenib alone

RT: radiotherapy, fx: fraction, OS: overall survival, CT: chemotherapy, SCCHN: head and neck squamous cell carcinoma, LR: locoregional, PFS: progression free survival, NSCLC: non small cell lung cancer; SBRT: stereotactic body radiotherapy; CRT: chemoradiotherapy; LRRFS: local-regional relapse-free survival.

SCCHN: A randomized phase-II trial evaluated the effect of erlotinib plus standard radiochemotherapy (cisplatin) on 204 patients with locally advanced SCCHN. Patients in experimental arm experienced more skin rash (any grade: 68% vs 10%, G3: 13% vs 2%). With a median follow-up of 26 months, erlotinib did not improve the pCR and DFS when added to cisplatin-RT. Outcome and toxicity findings were not age-related (Martins et al., 2013).

Another phase-II trial evaluated a novel combination of concurrent erlotinib, docetaxel and RT in the management of 43 LA-HNSCC patients. Median age was 57 years but patients were aged up to 75 years. The treatment regimen was feasible and the major local side effects noted were dysphagia, mucositis and dermatitis with a toxicity profile that was similar to standard chemoradiation. The median follow-up was 48.7 months; no difference for 3-year PFS, OS and local control was reported (Nguyen-Tan et al., 2014; Yao et al., 2016).

3.4.2. Esophageal cancer

Five studies were conducted recently to investigate the role of RT plus erlotinib/gefitinib in elderly patients with esophageal cancer, showing a median OS and PFS of 7–21 and 4.5–17 months respectively (Xu et al., 2015; Iyer et al., 2013; Zhai et al., 2013; Zhang et al., 2012; Song et al., 2017).

In a phase-II study, 33 elderly patients were treated with erlotinib and RT, showing a median OS and PFS of 16.3 and 16.7 months, respectively. 1- and 2-year OS rates were 66.3% and 49.7%. Toxicity was mild, mostly G1-2 (Zhang et al., 2012).

A Chinese study (Song et al., 2017) compared RT plus erlotinib versus concurrent CRT in 68 elderly esophageal cancer patients. RT plus erlotinib group showed a significant improvement in treatment compliance ($p = 0.016$) and a reduction of the average length of hospitalization ($p < 0.01$) compared with the CRT group. Overall, patients who received concurrent CRT suffered more from treatment-related toxicities. Conversely, patients who received erlotinib had higher rash events. No significant differences in terms of outcome were found between the two groups. The main type of treatment failure was locoregional for CRT group and distant metastasis for erlotinib-RT group (Song et al., 2017).

3.4.3. Brain metastases (BM)

The efficacy of concurrent TKIs plus whole-brain radiotherapy (WBRT) for patients with BM has been investigated, showing a significantly improve in disease control rate, OS (HR:0.72, 95%CI: 0.58-0.89) in patients with BM from NSCLC (Zheng et al., 2016). A Chinese retrospective study enrolled so far the highest percentage of brain metastatic elderly patients. Patients were randomized to receive either WBRT alone (92 cases) or WBRT with erlotinib/gefitinib (65 cases). Median age was 66 years (range: 35–81), 25% of patients were over 70 years old. The authors showed the same favorable toxicity profiles and clinical effects in the combination arm ($p < 0.05$), regardless of patients' age. Hematological and intracranial toxicities were similar between the two groups, whereas rash (47.7%), interstitial pneumonia (7.7%) and diarrhea (7.7) were observed only in the combination arm (Cai et al., 2013). Kim HJ et al. (Kim et al., 2015) retrospectively analyzed the outcome of stereotactic radiosurgery (SRS) (median dose of 23 Gy) and concurrent gefitinib/erlotinib for NSCLC-BM in 18 patients harboring an activating EGFR mutation. Median age was 55 years but patients up to 78 years old were included without observing any difference in terms of toxicity. However no benefit was demonstrated with this approach (Kim et al., 2015). Weickhardt et al. (Weickhardt et al., 2012) observed that in oligoprogressive EGFR-mutant patients aged up to 75 years, concomitant SRS or SBRT led to an additional 6 months of disease control with no relevant toxicity (Weickhardt et al., 2012).

3.4.4. Extra-cranial SBRT

A prospective phase-II trial enrolled 24 patients with median age 67 years receiving SBRT (19–24 Gy, 27–33 Gy or 35–40 Gy up to five fractions) and concurrent erlotinib until disease progression. Patients with no more than six sites of extracranial NSCLC disease who failed early systemic chemotherapy were enrolled. Four severe toxicity events were related to SRT (one G4 hypoxia that resulted in a G5 acute respiratory distress syndrome in the same patient 3 months after SBRT to three thoracic sites; one G3 vertebral body compression and one G3 radiation pneumonitis). The other three G4 toxicities (diarrhea and fatigue) were definitely related to erlotinib use. After a median follow-up of 11.6 months, median PFS and OS were 14.7 and 20.4 months, respectively. These results were substantially better than historical data for patients with stage IV NSCLC in this setting (2–4 months for median PFS; 6–9 months for median OS) (Iyengar et al., 2014).

3.4.5. Highlights

- *RT plus erlotinib/gefitinib with esophageal cancer is tolerable and effective.*
- *The combination of SBRT with gefitinib appears to be feasible and effective as the first-line treatment regimen for elderly patients with localized NSCLC, while in locally advanced NSCLC poor-risk patients is still controversial*
- *The association of WBRT or SRS with gefitinib/erlotinib for elderly patients with BM can significantly improve outcome without increasing toxicity.*
- *Gefitinib/erlotinib and extra-cranial SBRT seems to be associated with increased toxicity within the irradiated volume*

3.5. Sunitinib and Sorafenib

3.5.1. Renal cancer

Sunitinib and Sorafenib are considered the standard of care for metastatic renal cancer (mRCC), also in elderly patients (Albiges et al., 2015; Maroun et al., 2018). However, uncertainties remain about the feasibility of Sunitinib/Sorafenib in combination with RT regimens (Fiore et al., 2018).

In the study of Staehler et al (Staehler et al., 2012), 22 patients (median age 63 years) with mRCC were treated by RT plus sunitinib. Response to therapy was satisfactory, with a median follow up of 14.3 months, only 1 patient experienced a progression of disease. Only one G4 hypertension was reported, while skin toxicities were manageable with no G3 event (Staehler et al., 2012).

Sunitinib and RT for brain and spinal metastases (WBRT or SRS) seem to be feasible (Kusuda et al., 2011; Miller et al., 2016; Staehler et al., 2011). Miller el al. (Miller et al., 2016) showed that the co-administration of TKI with spine SBRT (16 Gy in 1 fraction) in 100 patients with mRCC improved the local control with a manageable toxicity (no Grade 3 toxicity; rate of fractures 21%; and pain exacerbation 17%). Median age of the population was 60 years with patients aged up to 87 years. Concurrent first-line TKI treatment with SRS remained independently predictive of superior local control (HR 0.21, $p = 0.04$) on multivariate analysis, with the highest rate of local failure in TKIs alone group (HR 2.43, $p = 0.03$) (Miller et al., 2016).

Staehler et al. (Staehler et al., 2011) analyzed outcomes for 106 patients with spinal or brain metastases from RCC. All patients, median age of 63 (range 27–84), were treated with SRS plus sorafenib/sunitinib. The 1- and 2-year local control rates were 94% and 90%, respectively. Even if no age-subgroup analysis was reported, no SRS-related toxicities ≥ G3 were observed for the entire population (Staehler et al., 2011).

3.5.2. Oligometastatic disease

In a single-arm Phase-I/II trial, (Kao et al. (2014)) reported his experience involving 46 patients treated with concurrent sunitinib and SBRT (mean dose 50 Gy) for oligometastatic disease. Seventy-four percent of the population was over 60, and 40% over 70 years.

Excellent results were obtained in terms of 4-year PFS and OS (34% and 29%, respectively). No ≥ G3 acute or late toxicity directly attributable to RT was observed (Kao et al. (2014)).

3.5.3. Hepatocarcinoma

The Wada study (Wada et al., 2017) evaluated 62 patients over 60 years, with metastatic hepatocellular carcinoma, treated with sorafenib plus fractionated RT (group RS) or sorafenib alone (group S). The overall incidence of adverse events were similar: 93.3% and 91.5% in RS and S group, respectively. On the contrary, incidence severe hematological and skin toxicity was higher in the RS group. NotablyOS and PFS were significant higher in RS group (Wada et al., 2017).

3.5.4. Highlights

- *Sunitinib and Sorafenib in combination with RT, especially SBRT, could be considered feasible and tolerable.*

3.6. Hedgehog signalling pathway inhibitor (HPI)

Vismodegib and sonidegib are HPI registered for the treatment of LA and metastatic basal cell cancer (BCC) patients. For the association with RT in elderly patients, literature data are based mainly on case reports.

Schulze et al (Schulze et al., 2016) reported 4 cases (3 cases over 71 years) where patients received vismodegib during and after definitive RT (50–55 Gy/20-28fractions). Two patients obtained a CR and one progressed after 6 months from RT. No serious or unexpected adverse reactions were observed: only two G3 toxicities occurred: a radiodermatitis, and a localized osteoradionecrosis of the mandible approximately 11 months after RT. All observed toxicities were predictable, and no specific side effects could be attributable to the RT-HPI combination (Schulze et al., 2016). Pollom et al (Pollom et al., 2015) presented the case of a 70 years old man affected by a recurring BCC of the left lower eyelid treated with neoadjuvant vismodegib, surgery and followed by concurrent RT (51 Gy/17 fractions) and vismodegib. The tolerance was good and the patient was disease-free after 12 months (Pollom et al., 2015).

Gathings et al. (2014) reported the case of a 81 years old man with multiple ulcerative BCC on his face, trunk, and extremities that started on vismodegib with a CR of several lesions after 10 weeks but a progression of those on the left parietal scalp, left zygoma, and left lower leg. The patient underwent RT to the left parietal scalp and left zygoma up to a total dose of 60 Gy and 40/48 Gy, respectively, with CR and no referred relevant toxicity (Gathings et al., 2014).

Data on sonidegib associated to RT are very poor. The BOLT trial is a phase II, randomized study, in patients with advanced BCC that evaluated once-daily doses of sonidegib 200 or 800 mg. Median age in the two arms were 67 and 65 years respectively. 24.1% and 32.5% of patients in the two arms received prior RT but no data of these patients were reported (Chen et al., 2018).

3.6.1. Highlights

- *The association of RT and HPI remains investigational.*

3.7. Immune check point blockade (ICIs)

The main issue on the efficacy of IT in elderly people is due to the age-related decline of the immune system, or immunosenescence (Tomihara et al., 2013), which may have a negative impact on the efficacy of ICIs. However, a recent metanalysis reported a significantly improved OS with ICIs alone also in elderly patients Nishijima et al. (2016).

To date many data underline the immune stimulation of RT, but findings regarding the association of ICIs/RT are scarce in the elderly population (Ngwa et al., 2018). Stokes et al (Stokes et al., 2017) retrospectively reported a longer OS (11 vs 6.3 months, $p < 0.01$) in patients with melanoma BM treated with RT plus IT. The subgroup analyses according to age (< 60, 60–69 and > 70) seemed to confirm the OS advantage for the entire population (Stokes et al., 2017).

3.7.1. Ipilimumab

Koller et al (Koller et al., 2017) retrospectively evaluated 101 patients treated with Ipilimumab +/- RT for advanced melanoma. Median age was 68 and 67 years (range: 31–91) for the two groups, respectively. Median OS and rates of CR were significantly increased in the concurrent arm. No increase toxicity was observed; no data correlated with age were reported (Koller et al., 2017).

Hiniker et al (Hiniker et al., 2016) prospectively analyzed 22 patients with stage IV melanoma treated with palliative RT and Ipilimumab. All the 11 elderly cases had a clinical benefit: 9 (82%) had a CR or partial response, 2 cases a stable disease (Hiniker et al., 2016).

Tazi et al. (2015) retrospectively evaluated the outcome of patients (median age 65 years) with metastatic melanoma treated with ipilimumab. All patients were stratified by presence or absence of BM, which were treated with SRS. A comparable survival between patients with or without BM was shown, in absence of significant difference in terms of toxicity. Based on the latter findings, the authors hypothesized that the addition of SRS may enhance ipilimumab-induced immune response (Tazi et al., 2015).

Boyer et al. (2016) retrospectively analyzed patients undergoing either definitive or post-operative RT enrolled in a prospective single-arm phase-II trial of neo-adjuvant ipilimumab for NSCLC. RT was well tolerated with no observed ≥ G3 side effects (Boyer et al., 2016).

A phase-III trial evaluated 799 patients with at least one bone metastasis from castration-resistant prostate cancer that had progressed after docetaxel. Patients were randomized to receive bone-directed RT (8 Gy/1fraction) followed by either ipilimumab or placebo. Median age was 69 and 67.5 years in the Ipilimumab and the placebo group, respectively. Overall, there was no significant difference between the two groups in terms of OS. Notably, in some subgroups of patients (with an alkaline phosphatase concentration of less than 1·5 times ULN, a haemoglobin concentration of 110 g/l or higher, and no visceral metastases), ipilimumab improved OS (Kwon et al., 2014).

Nivolumab/pembrolizumab: Shaverdian et al (Shaverdian et al., 2017), in a secondary analysis of Keynote-001 trial, evaluated the disease control and pulmonary toxicity in patients treated with/without RT for NSCLC before receiving pembrolizumab. Median age was 66 and 65 years (range: 32–83) for RT or non RT group respectively. Authors detected a significantly longer PFS and OS in RT group without increasing in side effects (Shaverdian et al., 2017). Nagasaka et al (Nagasaka et al., 2016) reported the case of a 66 years old woman with an unresectable locoregional recurrence of oral cavity SCC treated with several CT agents with no benefit. She was enrolled in a clinical trial utilizing pembrolizumab with stable disease and underwent to palliative RT (30 Gy/10 fractions) to the left neck nodes with an excellent clinical response. The authors suggest a synergistic effect of pembrolizumab and RT based on an active immune microenvironment that may maximize RT efficacy (Nagasaka et al., 2016). Regarding the potential risk of side effects, in elderly patients there are some case-report of pneumonitis related to the association of anti-PD1 and RT (Lu and Liu, 2017; Manapov et al., 2018; Shibaki et al., 2017; Yoshida et al., 2017).

3.7.2. Highlight

- *RT and Ipilimumab seems to improve outcomes especially for metastatic brain melanoma*
- *RT and anti-PD1 seems to give a beneficial effect in lung cancer but with a slightly higher risk of pneumonitis.*

4. Criticism and perspective

All studies considered in this review used an age cut off to identify elderly patients, no selection according to performance status or co-morbidity index has been performed. At the present time is growing the concept that elderly population is very heterogeneous and that chronological age is not a determining factor and biological age should be considered instead. It seems that, if adequately selected, subgroup of these patients may tolerate and present outcomes comparable to their younger counterpart. This selection is based on the use of geriatric tools that allow to stratify elderly population in different categories according to treatment-related risks: the final aim is to identify frail patients, tailoring the treatment on the single patient and subsequently selecting those patients in need of major care during and after treatment. Some recruiting trials continue to use an age cut off (usually patients > 65 or 70 years old as NCT02375581 or NCT03025958) but others (NCT03416244) require a geriatric evaluation (G8 > 14 points or CGA/DAFI 0.2 < 0.35) in inclusion criteria.

5. Conclusion

Radiotherapy and new TT/IT are crucial arms for fighting cancer, but, despite their large utilization, data for elderly patients are lacking. Considering this and the future increase in age cancer population, further trials are advocated to obtain clear data on association of RT and TT/IT, regarding tolerability but also time and dose administrations both for drugs and RT, in specific setting of elderly population.

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Declarations of interest

None.

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