Systemic treatment and radiotherapy for patients with non-small cell lung cancer (NSCLC) and HIV infection – A systematic review

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A B S T R A C T

Lung cancer is the most common non-AIDS defining cancer among people living with HIV (PLWH), but there is a paucity of data regarding the efficacy and toxicity of radiotherapy and systemic regimens, including immuno- therapy, in the treatment of these patients. In order to answer this question, we have performed a systematic search of the literature in Ovid Medline until March 17, 2022. We included 21 publications, enrolling 513 PLWH with non-small cell lung cancer (NSCLC), mostly male (75–100%), (ex-)smokers (75–100%) and with stage III-IV at diagnosis (65–100%).

The overall response rate (ORR) to chemotherapy (n = 186 patients, mostly receiving platinum-based regi-

mens) was highly variable (17 %–83 %), with a substantial hematological toxicity. ORR varied between 13 % and 50 % with single-agent immunotherapy (n = 68), with median overall survival between 9 and 11 months and a very acceptable toxicity profile, in line with studies in the HIV non-infected population. All five patients receiving tyrosine kinase inhibitors (TKIs; gefitinib or erlotinib) showed a partial response and long overall survival. Yet, combination of TKIs with antiretroviral therapy using pharmacological boosters, such as ritonavir, should be avoided. Radiotherapy was evaluated among 42 patients, showing high ORR (55 %–100 %), but 18 % of patients had a pneumonitis.

This systematic review shows that radiotherapy and systemic therapy are effective and safe among PLWH with controlled infection diagnosed with NSCLC. Nonetheless, most reports were small and heterogeneous and larger studies are needed to confirm these encouraging findings. Moreover, clinical trials should not restrict the in- clusion of PLWH, as more data is needed regarding the long-term efficacy and safety of treatments among this underserved population, especially of immunotherapy.

1. Introduction

HIV prevention and treatment is considered a priority health issue to the World Health Organization. Over 38 million people have a HIV diagnosis and it is estimated that over 650.000 people died of an HIV- related cause in 2021 [1]. In 1996, the introduction of highly active

antiretroviral therapy (ART) has completely changed the survival of people living with HIV (PLWH). Nowadays, PLWH under ART have a life expectancy comparable to HIV-negative people, thus increasing their probability of developing cancer [2]. Yet notably, some publications reported that PLWH with a cancer diagnosis did not receive a suitable oncological treatment [3–5]. Additionally, several clinical trials excluded PLWH or other viral diseases (i.e. hepatitis), limiting the po- tential oncological treatments offered to this population.

Lung cancer is the most common non-AIDS defining cancer among PLWH [6], with a standardized incidence ratio of 58.3 per 100,000 person-years in 2013–2016 in the US [7]. It is also the second largest contributor to death in PLWH among all cancers [8], with a population- attributable fraction of death of 2.4 %. Moreover, lung cancer-specific mortality is significantly higher among PLWH compared with HIV- uninfected patients – hazard ratio 1.28 (95 % confidence interval [CI] 1.17–1.39) in the study by Coghill et al [4]. Finally, in 2030, prostate and lung cancer, which are the most common cancers in the general population in the US, are projected to be the most common cancers in PLWH [9].

Therefore, it is important to understand which therapeutic strategies might be beneficial and safe for patients with both conditions. Moreover, as in the last years immunotherapy changed the therapeutic approach for several tumors, including non-small cell lung cancer (NSCLC), it is paramount to know if PLWH may be eligible for immunotherapy [10].

In this systematic review, we aimed to assess the efficacy and toxicity of radiotherapy and systemic regimens, including immunotherapy, in the treatment of patients with NSCLC and HIV infection.

2. Material and methods

A scientific librarian (VD), experienced in searching for medical and scientific publications, and two physicians (MB, NL), experts in the treatment of lung tumors performed a systematic search of the literature from inception up to March 17, 2022. SciVerse Scopus database and Ovid Medline database using the OvidSP interface were searched. The “Population, Intervention, Comparison, Outcome” (PICO) questions model for clinical questions was used to identify the concepts included in the questions. The corresponding search criteria of “P” and “I” were translated into MeSH terms and free-text keywords (Supplemental Table 1). Citations were exported from Medline and Scopus databases into reference manager software (EndNote) to allow the removal of duplicates and to facilitate the selection process performed by reviewers. All articles retrieved by the librarian selected for their eligibility by two authors based on the title and abstract and the final selection was per- formed by reading the full publication and its inclusion was consensu- ally decided. Reference lists of included studies and review articles were screened to identify additional publications. The standard reporting guidelines (Preferred Reporting Items for Systematic Reviews and meta-Analyses statement [PRISMA]) has been used for this systematic review [11].

Observational studies (case series, cohort studies, and registries) and prospective clinical trials were eligible if providing information on the efficacy and/or toxicity of systemic treatment and/or radiotherapy among patients with NSCLC and HIV infection. Only publications accessible to the authors for their language (English, French, Dutch, Spanish, Italian, and Portuguese) were deemed eligible.

When more than one publication reported the same endpoint for the same/potentially overlapping study population, we used data prefer- entially from the full publication (vs abstract), from the publication with the largest sample size or data corresponding to the longest follow-up period, as applicable.

2.1. Data extraction

Two reviewers independently evaluated the screened titles/abstracts; in case of disagreement, a third author resolved it. After this

initial screening, full papers were reviewed and the following variables were extracted: [1] study characteristics (design, patient selection); [2] patients' characteristics (gender, age, smoking status, performance sta- tus); [3] HIV-related information (CD4 + cells count, undetectable viral load, proportion of patients under ART); [4] stage at diagnosis of lung cancer; [5] type of anti-cancer treatment received and its respective efficacy and toxicity.

Efficacy was assessed as overall response rate (ORR; defined as the proportion of patients with complete or partial response according to RECIST criteria), progression-free survival (PFS; time from treatment start until progression or death) and overall survival (OS; time from treatment start until death, whichever the cause). In order to reduce heterogeneity, efficacy of systemic treatment was considered in the metastatic setting, while toxicity was assessed both in the early and in the metastatic setting.

When the study included patients with NSCLC and non-NSCLC tu- mors (including small-cell lung cancer [SCLC]), we extracted data spe- cifically for patients with NSCLC. Nonetheless, there were some studies that included a small proportion of patients with SCLC and did not report separately NSCLC from SCLC patients [12–16] – in these situa- tions, we extracted information regarding all patients with lung cancer, given that patients with NSCLC constituted the large majority of cases.

2.2. Quality assessment and publication bias

A quality assessment was performed based on study design, patient selection, adequate description of the treatments received, reporting of response according to RECIST criteria and of toxicity according to CTCAE criteria, and median follow-up. In each category, risk was clas- sified from "low" to "high".

2.3. Data synthesis

Given the high heterogeneity of the selected studies in terms of pa- tient inclusion, type of treatments and presentation of results, a quan- titative synthesis of results was not feasible and, therefore, a *meta*- analysis was not performed.

3. Results

3.1. Characteristics of included studies

The systematic search of literature provided 776 unique citations, of which 85 were reviewed as full text (Fig. 1). An additional study was retrieved after cross-referencing. Among them, 21 studies, published between 1998 and 2021 were included: 12 assessed the efficacy and/or toxicity of chemotherapy [12–23], six described immunotherapy [24–29], three reported on tyrosine kinase inhibitors (TKIs) [20,30,31], and eight assessed radiotherapy [13–17,20,22,32]. They included a total of 543 patients with lung tumors, of which 513 with NSCLC.

Four of the studies were from North America (all from the USA) [14,24,26,28], 11 from Europe [12,17,18,25,31,29], one from Europe and the USA [13], and 5 from Asia (all from Japan) [16,20,21,30,32] – Table 1.

Studies' quality assessment is provided in the appendix (Supple- mental Table 2). There were only four prospective clinical trials [18,25,28,29] and two prospective observational studies [17,23]. There was a high variation on reporting of radiotherapy and chemotherapy, with different regimens and doses being analyzed simultaneously. Regarding radiotherapy, most studies did not report the total dose administered to patients nor the technique used [13,15,17,22,32].

3.2. Baseline characteristics

Patients were generally young at diagnosis (median age between 43 and 66 year-old), most were male (75–100 %), (ex-)smokers (75–100

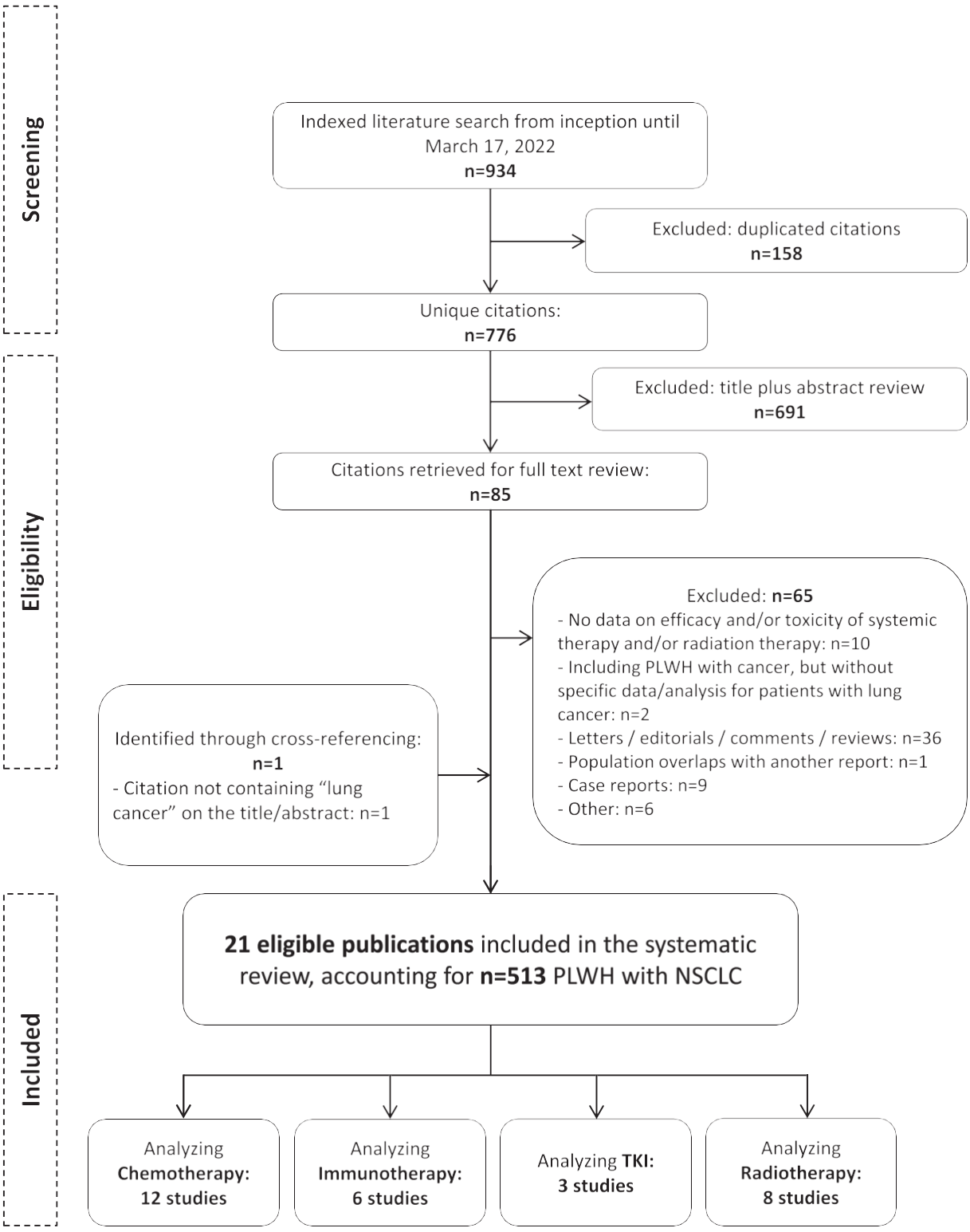

Fig. 1. Study selection flow chart. NSCLC: non-small cell lung cancer; PLWH: people living with HIV; TKI: tyrosine kinase inhibitors.

%), had a performance status of 0–1 (22–100 %) and presented with stage III-IV at diagnosis (65–100 %).

Patient inclusion dates spanned from 1986 to 2019, including pa- tients both before and after the introduction of ART, in 1996. Therefore, there was a wide variation on CD4 + cell counts, and on the proportion of patients under ART at the time of cancer diagnosis (25–100 %) and with undetectable viral load (0–100 %). ART regimen was reported in six (out of 10) chemotherapy studies and in four (out of six) immuno- therapy studies. In the chemotherapy studies (published during 2004–2012), 35 %-52 % of the ART regimens were based on protease inhibitors, but the use of integrase strand transfer inhibitors (INSTIs) was not reported [12–15,19,20]. On the other hand, in the more recent

studies concerning immunotherapy (published during 2018–2020), 17–28 % of patients were on protease inhibitors, while 25 %-85 % were on INSTIs [24,26,27,29].

3.3. Efficacy and toxicity of radiotherapy

Among 42 patients receiving radiotherapy, either solely or in com- bination with chemotherapy, ORR was only reported in three studies, including 16 patients [13,20,22], and it varied between 55 % and 100 % (Table 2). Median OS ranged from 3 to 43 months. Regarding pneu- monitis, there were two cases of grade 1–2, two cases of grade 3–4, as well as one fatal case of pneumonitis (grade 5).

Table 1
Characteristics of the included studies.

Author – study name (Year)	Location	Region	LC only?	Study design	Inclu-sion dates	Nb of LC patients*	ART (%)	CD4 + cell count (cell/mm³) – median (range)	UVL (%)	Age – median (range)	PS 0–1 (%)	Male s (%)	Stage III-IV (%)	(Ex)-Smokers (%)
Peyrade (1998) (22)	France/ Nice	Europe	Yes	Retrospective, unicentric	1987–1997	15	NR	240 (0–510)	NR	45 (30–86)	NR	100 %	100 %	100 %
Powles (2003) (23)	UK/ London	Europe	Yes	Prospective, unicentric	1996–2002	9	78 %	160 (136–890)	33 %	45 (32–58)	22 %	NR	100 %	NR
Spano (2004) (15)	France/ Paris	Europe	Yes	Retrospective, multicentric	1993–2002	22 (21 NSCLC)	86 %	364 (20–854)	24 %	45 (33–64)	69 %	86 %	73 %	95 %
Lavole (2009) (17)	Paris/ France	Europe	Yes	Prospective, multicentric	1996–2007	49	73 %	350 (3–1580)	35 %	46 (34–70)	71 %	86 %	84 %	100 %
D'Jaen (2010) (13)	USA + UK	North America + Europe	Yes	Retrospective, multicentric	1996–2008	75 (65 NSCLC)	80 %	340 (0–1456)	65 %	50 (32–75)	NR	83 %	77 %	99 %
Kaminuma (2010) (32)	Tokyo/ Japan	Asia	No	Retrospective, unicentric	1997–2009	2	100 %	*82 (11–561)* [Δ]	NR	*51 (29–70)* [Δ]	NR	*96 %* [Δ]	NR	NR
Makinson - Dat'Aids (2011) (19)	France	Europe	Yes	Retrospective, multicentric	1996–2008	52	90 %	300 (25–1551)	56 %	48 (32–77)	65 %	81 %	90 %	98 %
Okuma (2012) (21)	Tokyo/ Japan	Asia	Yes	Retrospective, unicentric	1985–2010	13	77 %	332 (52–682)	62 %	59 (39–73)	85 %	100 %	77 %	92 %
Pakkala (2012) (14)	USA/ Atlanta	North America	Yes	Retrospective, multicentric	1995–2008	80 (73 NSCLC)	55 %	304 (3–1361)	28 %	52 (28–73)	62 %	80 %	80 %	100 %
Okuma (2013) (20)	Japan	Asia	No	Retrospective unicentric	NR	2	Both	425 & 404	Both	66 & 69	NR	Both	100 %	NR
Bearz (2014) (12)	Italy	Europe	Yes	Retrospective, multicentric	1986–2003	68 (58 NSCLC)	50 %	Pre-ART: 278 (12–987); post-ART: 339 (4–761)	29 %	43.5 (31–68)	63 %	90 %	85 %	94 %
Okuma (2015) (30)	Tokyo/ Japan	Asia	Yes	Retrospective, unicentric	NR	2	100 %	404 & 120	Yes & No	59 & 67	NR	Both	100 %	Both
Cr´equit (2016) (31)	France	Europe	Yes	Retrospective, multicentric	1996–2013	2	100 %	300 & 480	0 %	49 & 60	50 %	100 %	100 %	100 %
Takahashi (2017) (16)	Tokyo/ Japan	Asia	Yes	Retrospective, unicentric	1988–2015	20 (19 NSCLC)	25 %	373.5 (52–635)	45 %	61 (39–77)	90 %	100 %	65 %	95 %
Chang (2018) (24)	USA	North America	No	Retrospective, multicentric	2015–2017	8	100 %	284 (63–915)	38 %	66 (56–85)	NR	100 %	NR	75 %
Ostios-Garcia (2018) (65)	Boston/ USA	North America	Yes	Retrospective, unicentric	NR	7	86 %	360 (57–1147)	86 %	52 (43–59)	NR	86 %	100 %	100 %
Spano – CANCERVIH (2019) (27)	France	Europe	No	Retrospective multicentric	2014–2019	21	100 %	370 (IQR 125–1485)	100 %	62 (IQR 52.5 –68.5)	87 %	78 %	NR	NR
Uldrick (2019) (28)	USA	North America	No	Phase 1 trial, single-arm	2016–2018	2	100 %	285 (132–966)	*87 %* [Δ]	*57 (39–77)* [Δ]	100 %	*93 %* [Δ]	100 %	NR
Gonzalez-Cao (2020) (29)	Spain	Europe	No	Prospective, multicentric	2017–2018	20 (16 NSCLC)	100 %	*95 % with CD4+ ≥ 200 cell/mm³* [Δ]	100 %	*54 (30–73)* [Δ]	*95 %* [Δ]	*80 %* [Δ]	100 %	NR
Lavole (2020) – IFCT-1001 CHIVA (18)	France	Europe	Yes	Phase 2 trial, single-arm	2011–2016	61	95 %	418 (18–1230)	80 %	53 (36–67)	80 %	75 %	100 %	93 %
Lavole (2021) – IFCT-1602 CHIVA2 (25)	France	Europe	Yes	Phase 2 trial, single-arm	2017–2019	16	100 %	385 (187–778)	100 %	58 (44–71)	75 %	88 %	100 %	100 %

*Number of patients with thoracic tumors. If no indication is provided, all patients have NSCLC. When there is an inclusion of patients with both NSCLC and patients with other thoracic tumors, the number of patients with NSCLC is provided in parenthesis.

[Δ] Values in italic mean that the value refers to the entire study population and not specifically to patients with NSCLC.

ART: anti-retroviral treatment; IQR: interquartile range; LC: lung cancer; NR: not reported; PS: performance status; UVL: undetectable viral load (different definitions according to each study).

Table 2
Efficacy and toxicity of radiotherapy (RT) among people living with HIV (PLWH) with non-small cell lung cancer (NSCLC) – grading according to CTCAE.

Author (year)	Nb pts	Regimens	ORR (%)	SD (%)	PD (%)	Median OS	Median PFS	Median FU	% G1-G2 Pneumonitis	% G3-G4 Pneumonitis	% G3-G4 tox other	% G5 tox
Peyrade (1998) (22)	3	RT alone (dose NR)	2 (67 %)	1 (33 %)	0	9 (range 5–24)	NR	NR	NR	NR	NR	NR
Spano (2004) (15)	2	Chemo-RT (n = 1) & RT alone (n = 1)	NR	NR	NR	7 & 3	NR	NR	0	0	0	0
Lavole (2009) (17)	5	Concomitant chemo-RT (dose and regimens NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (20 %) - Pneumonitis
D'Jaen (2010) (13)	11	RT alone (dose NR)	6 (55 %)	1 (9 %)	4 (36 %)	NR	NR	NR	NR*	NR*	NR*	NR*
Kaminuma (2010) (32)	2	RT alone (dose NR)	NR	NR	NR	NR	NR	NR	0	0	0	0
Pakkala (2012) (14)	14	Platinum-based chemotherapy (multiple regimens) + concomitant RT (total dose between 34 and 66 Gy)	NR	NR	NR	NR	NR	NR	0	0	NR¥	1 (7 %) – Sepsis & respiratory fail
Okuma (2013) (20)	2	Cisplatin-docetaxel + concomitant RT (total dose 59.4 Gy) (n = 1) Carboplatin-paclitaxel + concomitant RT (total dose 60 Gy) → consolidation chemotherapy (n = 1)	2 (100 %)	0	0	38 & 43	38 & 11	38 & 43	2 (100 %)	0	0	0
Takahashi (2017) (16)	3	Platinum-based chemotherapy (alone or with a taxane) + concomitant RT (total dose between 58 and 60 Gy)	NR	NR	NR	NR	NR	NR	0	2 (67 %)	2 (67 %)	0

* Of the 56 PLWH-NSCLC patients who received 1st-line CT or RT, 63% experienced treatment-related adverse events, including 19 (34%) with grade III or grade IV adverse events. Of the hematologic toxicities reported with initial chemotherapy, over a third resulted in hospitalization.
¥ Grade 3 or 4 toxicities occurred in in 9 of 15 patients (60%; including one patient with small-cell lung cancer) who received chemoradiation.
FU: follow-up, in months; NR: not reported; ORR: objective response rate, comprising complete response and partial response; OS: overall survival, in months; PD: progressive disease; PFS: progression-free survival, in months; SD: stable disease.

3.4. Efficacy and toxicity of systemic therapy

3.4.1. Chemotherapy

Chemotherapy efficacy was evaluated in nine studies [13,15–19,21–23], only one of them being a prospective clinical trial [18] – Table 3. Of the 186 patients with advanced NSCLC (stage III/IV), most received platinum-based chemotherapy (the standard-of-care at the time of conduction of these studies), but also single-agent chemo- therapy (i.e. taxanes, among others). The ORR was highly variable (between 17 % and 83 %), probably due to the low number of patients in each study, and to patient and treatment heterogeneity. As seen in Fig. 2, larger studies presented lower ORR. Median OS was modest, going from 2 to 15 months. Only the prospective trial by Lavole et al. reported on PFS, which was of 3.5 months (95 % CI 2.7–4.4) with an induction chemotherapy by carboplatin-pemetrexed, followed by maintenance pemetrexed [18].

Grade 3–4 hematological toxicity from chemotherapy was substan- tial, with one series reporting up to 88 % (Table 4). Nonetheless, toxic deaths were exceptional. No study reported if prophylaxis of pneumo- cystis was administered or not to patients.

3.4.2. Immunotherapy

Single-agent immunotherapy with nivolumab or pembrolizumab was assessed in three prospective trials [25,28,29] and three retro- spective case series [24,26,27], with a total of 68 patients with NSCLC. Immunotherapy was given from 1st to 3rd line of therapy in most of the

studies, with an ORR varying from 13 % to 50 % and with a median OS between 9 and 11 months. The proportion of patients experiencing immune-related adverse events (irAEs) varied from 28 % to 43 % in the retrospective series to 43 %-75 % in the prospective trials, but mostly consisted of grade 1–2 toxicity. Notably, there were no opportunistic infections nor immune reconstitution inflammatory syndromes reported and there was no detrimental effect on CD4 + cell counts nor on viral load [24,25,28,29]. There was a case of multicentric Castleman disease in a patient with Kaposi sarcoma treated by pembrolizumab in the trial

by Uldrick et al., but this has not been in seen among patients with NSCLC [28].

3.4.3. Tkis

The efficacy of EGFR TKIs was evaluated in two case series, both with two patients each [30,31] and there was one patient in the series by Okuma et al [20] that received erlotinib upon relapse. All of these pa- tients showed a partial response to TKIs, had PFS between 10 and 29 months and a long OS (from 28 months to not reached). All patients presented a mild rash, which is expected with these agents, except one of them, who experienced a severe rash due to the interaction between erlotinib and the pharmacological booster ritonavir [31]. Interestingly, this patient was re-challenged by gefitinib several months later, with good tolerance and a long-lasting response.

Table 3
Efficacy of systemic therapy among people living with HIV with advanced non-small cell lung cancer (NSCLC).

Author (year) *	Nb of eval NSCLC pts	Regimens	Line of therapy Δ	ORR (%)	SD (%)	PD (%)	Median OS	1-year OS (%)	Median PFS	Median FU
Chemotherapy										
Peyrade (1998) (22)	6	NR	1	1 (17 %)	0	5 (83 %)	2 (range 1–24)	NR	NR	NR
Powles (2003) (23)	8	Mitomycin-vincristine-cisplatin or gemcitabine-carboplatin	1	4 (50 %)	2 (25 %)	2 (25 %)	5 (range 2–15 +)	11 %	NR	NR
Spano (2004) (15)	11	Platinum-based CT	1	NR	NR	NR	7 (range 3–24)	NR	NR	NR
Lavole (2009) (17)	24	Platinum-based	1	14 (60 %)	SD + PR: 10 (40 %)		NR	NR	NR	NR
D'Jaen (2010) (13)	25	Platinum salt + taxane (45 %), gemcitabine (26 %), or vinca alkaloid (10 %). Other treatment regimens: mitomycin, vinorelbine, and cisplatin (13 %), single-agent CT (6 %)	1	10 (40 %)	1 (4 %)	14 (56 %)	NR	NR	NR	NR
Makinson (2011) (19)	40	Platinum-based or docetaxel	*1 (65 %) to 3+* Δ	NR	NR	NR	16.3	NR	NR	13.3
Okuma (2012) (21)	6	Platinum-based CT	1	5 (83 %)	0	1 (17 %)	14 (range 3–17)	66.7 %	NR	NR
Takahashi (2017) (16)	5	Platinum-based CT	1	3 (60 %)	SD + PR: 2 (40 %)		14.8 (95 % CI 2.5–46)	NR	NR	NR
Lavole (2020) (18)	61	Carboplatin-pemetrexed → maintenance pemetrexed	1	13 (21 %)	18 (30 %)	30 (49 %)	7.6 (95 % CI 5.7–12.8)	NR	3.5 (95 % CI 2.7–4.4)	45.5
Immunotherapy										
Chang (2018) (24)	7	Nivolumab	2	1 (14 %)	1 (14 %)	5 (71 %)	NR	NR	2.75	NR
Ostios-Garcia (2018) (65)	7	Nivolumab or pembrolizumab	1–3	3 (43 %)	2 (29 %)	2 (29 %)	NR	NR	NR	NR
Spano (2019) (27)	21	Nivolumab or pembrolizumab	1–3	4 (19 %)	5 (24 %)	12 (57 %)	10.7 (IQR: 8.4–15.9)	NR	NR	10.8 (range 2.0–27.7)
Uldrick (2019) (28)	2	Pembrolizumab	*Median: 3 (1–9)* Δ	1 (50 %)	SD or PR: 1 (50 %)		NR	NR	NR	NR
Gonzalez-Cao (2020) (29)	11	Durvalumab	*1 (40 %) to 3+* Δ	4 (36 %)	3 (27 %)	4 (36 %)	*9.2 (95 % CI 2.3-NotR)* Δ	NR	*2.4 (95 % CI 1.4–5.3)* Δ	*12.7*
Lavole (2021) (25)	15	Nivolumab	2–3	2 (13 %)	8 (53 %)	5 (33 %)	10.9 (95 % CI 2.2-NotR)	NR	3.4 (95 % CI 1.8–5.6)	23.6
Tyrosine kinase inhibitors										
Okuma (2013) (20)	1	Erlotinib	2	1 (100 %)	0	0	32	100 %	NA	NR
Okuma (2015) (30)	2	Erlotinib & Gefitinib	1	2 (100 %)	0	0	28 & NR	100 %	9.7 & 22.1	NR
Cr´equit (2016) (31)	2	Erlotinib & Erlotinib followed by Gefitinib	2	2 (100 %)	0	0	29.7 & 75.3	100 %	14 & 29	NR

*Authors in bold means that the study is a prospective clinical trial.
Δ Values in italic mean that the value refers to the entire study population and not specifically to patients with NSCLC.
CI: confidence interval; CT: chemotherapy; FU: follow-up, in months; IQR: interquartile range; NotR: not reached; NR: not reported; ORR: objective response rate, comprising complete response and partial response; OS: overall survival, in months; PD: progressive disease; PFS: progression-free survival, in months; SD: stable disease; TKI: tyrosine kinase inhibitors.

4. Discussion

Lung cancer is the most common non-AIDS defining malignancy among PLWH. Overall, lung cancer comprises around 20 % of the cancer burden in the US among PLWH [6]. Its incidence has been increasing among PLWH, due to multiple factors. Firstly, the high smoking prev- alence in this population [6,33]. Accordingly, 75–100 % of the patients

included in the present systematic review were (ex-)smokers. Secondly, thanks to widespread ART use, ageing is common in all cohorts world- wide. Thirdly, some studies also suggest that immunosuppression (assessed by low current CD4 + cell counts) and/or chronic pulmonary inflammation arising from recurrent infections might contribute also to this increasing incidence [33–36].

Importantly, evidence indicate that the prognosis of PLWH might be

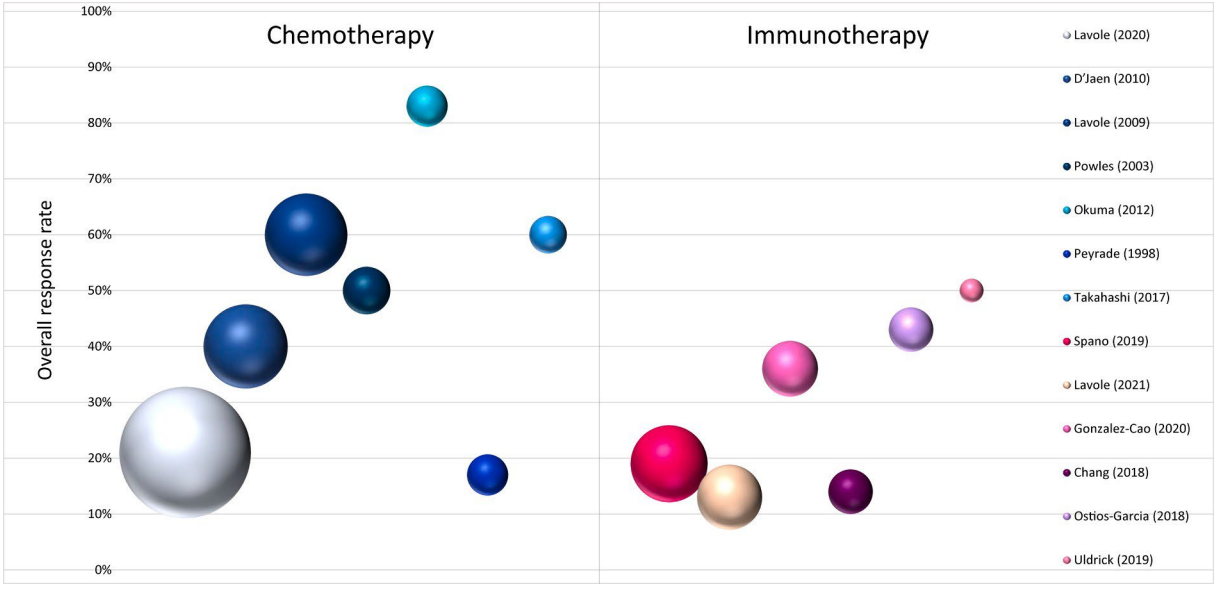

Fig. 2. Overall response ratio of studies evaluating chemotherapy (left panel) and immunotherapy (right therapy) for people living with HIV (PLWH) and non-small cell lung cancer. The size of each bubble is proportional to the number of PLWH included in each study. Studies are arranged in descendant order, from the studies with the larger sample size (at the left of each panel) to the smaller sample size (on the right).

worse after NSCLC diagnosis [37], in line with studies assessing other non-AIDS defining malignancies [38]. A large cohort study from the US showed that lung cancer-related survival is lower among PLWH compared to HIV-negative patients (5-year survival of 9.5 % vs 19.3 % respectively, p = 0.002). This difference was significant even after adjusting for age, race/ethnicity, stage, cancer treatment type, and smoking status, with a hazard ratio of 1.3 (95 % CI 1.0–1.7, p = 0.046) [37]. Importantly, the authors showed important differences in treat- ment patterns: only 64 % of PLWH received any cancer treatment compared to 76 % of the HIV-negative patients. The same held true for the receipt of chemotherapy (39 % vs 49 % of patients, respectively).

Therefore, our systematic review is important because it shows that patients with lung cancer and HIV infection also benefit from radio- therapy and different systemic treatments, such as chemotherapy, immunotherapy and TKIs.

4.1. Radiotherapy

Conventional radiotherapy, usually combined with chemotherapy, is the mainstay of treatment for most patients with stage III NSCLC [39]. Despite these generalized use, there is still a paucity of data regarding its efficacy and toxicity among PLWH [5]. In this systematic review, we analyzed these outcomes among a sample of only 42 patients, but which is the larger number reported in the literature. ORR was generally high (55 %–100 %), but OS was highly variable, ranging from 3 to 43 months. A total of 18 % of patients (5 out of 28) presented pneumonitis, but given the small number of patients, it is difficult to assess if this proportion is higher than expected in the "general population" or not. Moreover, there was scarce data on the radiotherapy doses used, as well as on the techniques, which limits the extrapolation of these data to the current clinical setting. Thus, larger cohort/multicentric studies are needed to assess the efficacy and toxicity of radiotherapy in the management of NSCLC in PLWH.

4.2. Chemotherapy

Regarding chemotherapy, the IFCT-1001 CHIVA trial, the only prospective study testing induction treatment by carboplatin-pemetrexed followed by maintenance pemetrexed in PLWH [18] has shown similar results to the control arm of the KEYNOTE-189 trial (carboplatin-

pemetrexed-placebo) [40] in terms of ORR: 21 % and 19.4 %, respec- tively. Likewise, the median PFS was 3.5 (95 % CI 2.7–4.4) months among PLWH and 4.9 (95 % CI 4.7–5.5) months among HIV-negative individuals in the KEYNOTE-189 trial. Finally, median OS was 7.6 (95 % CI 5.7–12.8) in the CHIVA and 10.7 (95 % CI, 8.7–13.6) months,
respectively. Although the confidence intervals overlap, the numerically higher OS in the KEYNOTE-189 study might be related to patient characteristics (e.g. less comorbidities), but also to the fact that patients in this trial had the possibility of crossing-over to pembrolizumab upon progression, while the PLWH in the CHIVA trial did not. Curiously, two series from Japan [16,21] and one from France [19] reported median OS superior 12 months with platinum-based chemotherapy, but these might be due to selection bias (i.e. only “very fit” PLWH were eligible for chemotherapy).

There seems to be an improvement in survival over time among patients receiving chemotherapy, maybe linked to an increasing use of ART but also of more effective systemic therapies, such as platinum- based chemotherapy. Yet, there is no correlation between immuno- therapy or TKI efficacy and time point, most likely because these are recent therapies, thus the timespan between the oldest and the most recent study is short.

Even so, it is important to note that chemotherapy might indeed cause substantial hematological toxicity among PLWH. In the CHIVA trial [18], 60 % of patients experienced grade 3/4 hematological toxicity, while this was the case for 43 % in the KEYNOTE-189 trial control arm [40]. In the retrospective series assessing platinum-based chemotherapy, grade 3/4 hematological toxicity varied from 19 % to 88 % [13,15–17,19,21–23].

This variation might be due to low CD4 + cell counts in some patients as well as possible drug-drug interaction between ART and chemo- therapy agents. Although reports of these interactions are scarce, it is known that some ART agents may increase or decrease concentrations of anticancer drugs through cytochrome *P* (CYP) 450-related induction or inhibition [41]. This is especially relevant for ART using pharmacolog- ical boosters (such as cobicistat or protease inhibitors), which inhibit CYP3A4, explaining why in the series by Makinson et al [19], the use of protease inhibitors was the only variable significantly associated with a grade 4 hematological toxicity in the multivariable model (odds ratio 5.22, 95 % CI 1.07–25.38). Thus, use of CYP3A4-metabolized cytotoxic compounds such as docetaxel, vinorelbine or etoposide should be

Table 4
Toxicity of anticancer systemic treatment among people living with HIV (PLWH) with non-small cell lung cancer (NSCLC) – grading according to CTCAE.

Author (year) *	Nb of eval NSCLC pts	Anticancer Regimens/ART regimens reported (yes or no)	% tox G3-G4 Neutrop	% tox G3-G4 Anemia	% tox G3-G4 Plat	% tox G3-G4 hemat overall	% tox G3-G4 Non-hemato	% tox G5	% irAEs overall	Notes
Chemotherapy										
Powles (2003) (23)	8	Platinum-based CT/*not reported*	NR	NR	NR	4 (50 %)	NR	0	NA	–
Spano (2004) (15)	16	Neoadjuvant platinum-based CT (n = 2) & Platinum-based CT + concomitant RT (n = 2) & Platinum-based CT only (n = 12)/*reported*	2 (13 %)	NR	NR	NR	NR	0	NA	–
Bearz (2014) (12)	68	CT-RT (n = 25) & CT only (n = 43)/*reported*	NR	NR	NR	13 (19 %)	0	0	NA	–
D'Jaen (2010) (13)	25	Platinum-based CT & single-agent CT/*reported*	NR	NR	NR	NR	NR	NR	NA	£
Makinson (2011) (19)	40	Platinum-based CT or Docetaxel/*reported*	10 (25 %)	3 (8 %)	1 (3 %)	13 (33 %)§	NR	0	NA	–
Okuma (2012) (21)	8	Adjuvant CT (n = 2) & Platinum-based CT + concomitant RT (n = 2) & Platinum-based CT only (n = 4)/*not reported*	4 (50 %)	0	1 (13 %)	5 (63 %)	0	0	NA	–
Pakkala (2012) (14)	22	Platinum-based CT + concomitant RT (n = 14) & Platinum-based CT only (n = 8)/*reported*	4 (18 %)	2 (9 %)	NR	6 (27 %)	7 (32 %)	1 (7 %) – Sepsis & resp fail	NA	Not clear in terms of toxicity grading and relation
Okuma (2013) (20)	2	Platinum-taxane + concomitant RT/*reported*	0	0	0	0	0	0	NA	All grade 2
Takahashi (2017) (16)	8	Platinum-based CT + concomitant RT (n = 3) & Platinum-based CT only (n = 5)/*not reported*	6 (75 %)	0	2 (25 %)	7 (88 %)	5 (63 %)	0	NA	–
Lavole (2020) (18)	61	Carboplatin-Pemetrexed → maintenance Pemetrexed/*not reported*	32 (53 %)	18 (30 %)	21 (35 %)	36 (60 %)	13 (22 %)	1 (3 %) – sepsis	NA	AIDS history the only risk factor of G3–4 haematological toxicity
Immunotherapy										
Chang (2018) (24)	7	Nivolumab/*reported*	NR	NR	NR	NR	1 (14 %)	0	2 (29 %)	Hypothyroiditis G2 + Pneumonitis G3
Ostios-Garcia (2018) (65)	7	Nivolumab or pembrolizumab/ *reported*	0	0	0	0	0	0	3 (43 %)¶	No opportunistic infections or IRIS
Spano (2019) (27)	18	Nivolumab or pembrolizumab/ *reported*	0	0	0	0	2 (11 %)	0	5 (28 %)	Including G3 neurosyphilis
Uldrick (2019) (28)	All included pts (n = 30)	Pembrolizumab/*not reported*	0	*4 (13 %)* Δ	0	*4 (13 %)* Δ	*6 (20 %) – any tox*	*1 (3 %)*†	*13 (43 %)* Δ	No detrimental effect on CD4 + *T*-cell counts
Gonzalez-Cao (2020) (29)	All included pts (n = 20)	Durvalumab/*reported*	0	0	0	0	0	0	*15 (75 %)* Δ	All grade 1–2 diarrhea and arthralgia
Lavole (2021) (25)	15	Nivolumab/*not reported*	0	0	0	0	1 (6 %)	0	12 (75 %)¥	–
Tyrosine kinase inhibitors										
Okuma (2015) (30)	2	Erlotinib & Gefitinib/*reported*	0	0	0	0	0	0	0	Mild rash only
Cr´equit (2016) (31)	2	Erlotinib & Erlotinib followed by Gefitinib/*reported*	0	0	0	0	1 (50 %)	0	0	G3 rash due to interaction between erlotinib and ritonavir

*Authors in bold means that the study is a prospective clinical trial.
£ "Of the 56 PLWH-NSCLC patients who received 1st-line CT or RT, 63% experienced treatment-related adverse events, including 19 (34%) with grade III or grade IV adverse events. Of the hematologic toxicities reported with initial chemotherapy, over a third resulted in hospitalization".

¥ Mostly of grade 1 and 2 toxicity, except for one patient experiencing grade 3 pruritus, onycholysis, and pemphigoid; no opportunistic infections or unexpected irAE.
§ Grade 4 hematological toxicity only.
¶ All with grade 1–2 arthralgia.
† KSHV-associated inflammatory cytokine syndrome.
ΔValues in italic mean that the value refers to the entire study population and not specifically to patients with NSCLC.
CT: chemotherapy; irAE: immune-related adverse events; NA: not applicable; NR: not reported; RT: radiotherapy; TKI: tyrosine kinase inhibitors.

carefully monitored in patients receiving pharmacological boosters. One potential preventive measure is the administration of granulocyte colony-stimulating factors or switching to a "drug-drug interaction free" ART regimen.

Moreover, there is still a debate on the use of opportunistic infections prophylaxis among PLWH undergoing antineoplastic systemic treat- ment. The European AIDS Clinical Society recommends that systematic prophylaxis of fungal infections and pneumocystis should be given to all PLWH undergoing chemotherapy, regardless of the CD4 + cell levels at baseline [42]. On the other hand, the NCCN guidelines recommend it based on CD4 + cell levels and on the anticipated immunosuppression/ myelosuppression degree induced by chemotherapy [43]. Yet, real- world data is scarce on this topic. A large study among US veterans did not find an increased likelihood of opportunistic infections among
PLWH with HIV controlled disease undergoing chemotherapy compared to HIV-negative controls [44]. Of note, in this systematic review, there were no reported cases of opportunistic infections among PLWH and lung cancer treated with chemotherapy or immunotherapy, but we have no data regarding the use of prophylaxis for these infections. Still, this information might be useful for future guidelines on the topic, as it re- inforces the notion that PLWH receiving systemic anticancer treatment are not at a higher risk of developing opportunistic infections if their HIV disease is well-controlled.

Finally, non-hematological toxicity should also be considered, such as renal toxicity. For instance, nephrotoxicity of tenofovir and cisplatin may be additive, as both compounds induce tubular toxicity [41]. Likewise, the combination of pemetrexed and tenofovir may lead to renal toxicity, such as reported in the prospective CHIVA trial [18].

However, we should keep in mind that interactions between chemotherapy and ART remain mostly unpredictable, given the scarce data for individual compounds in the same drug class and their variable pharmacokinetic profiles and the fact that CYP450 drug metabolism may be partly related to the patient's genetic polymorphisms [45]. Therefore, the choice of chemotherapy regimens for PLWH should be discussed between the oncologist and the HIV-caring physician, taking into consideration the clinical and antiretroviral history, in order to select the most effective and least toxic combination. Moreover, the
European AIDS clinical society guidelines currently recommend CD4 + cell count testing in PLWH diagnosed with cancer one month after completion of chemotherapy treatment, in order to assess late toxicity [42].

4.3. Tkis

The only study assessing the prevalence of *EGFR* mutations in a PLWH-NSCLC cohort from France showed that it was only of 3.3 % [31]. This is not surprising, given that these patients were mostly male, Caucasian and former or current smokers. Still, both this French study and the Japanese reports [20,30] show that PLWH with *EGFR*-driven lung cancer largely benefited from EGFR TKIs, with high ORR and long survival rates, consistent with the clinical trials in the same setting [46,47]. Despite these encouraging results, there are no data regarding the use of osimertinib among PLWH, which is now the standard-of-care EGFR TKI in the first-line metastatic setting and which is also approved as adjuvant treatment in several countries [10,39]. Likewise, there is no data regarding the combination of erlotinib with anti-angiogenic agents such as ramucirumab, which may also be used for the treatment of these patients [48].

As discussed before regarding chemotherapy, potential interactions

might also exist between TKIs such as erlotinib and gefinitib and phar- macological boosters, namely with ritonavir, the most potent inhibitor in the protease inhibitors class, as both drug classes are extensively metabolized by the CYP enzymes. Therefore, protease inhibitors should be discouraged among patients proposed for these TKIs, as the TKIs excessive concentration may induce severe skin reaction and life- threatening pneumonitis. As the CYP3A4 enzymes metabolize osi- mertinib, the concurrent use of protease inhibitors should also be avoided.

4.4. Immunotherapy

Finally, our review is the largest one including specifically PLWH with NSCLC receiving immunotherapy. Among the 68 patients included, we have seen that single-agent immunotherapy with nivolumab, pem- brolizumab or durvalumab is both effective and safe [24–29]. The IFCT- 1602 CHIVA2 prospective phase II trial [25] was specifically designed for these patients, receiving 2nd or 3rd-line single-agent nivolumab, while in the DURVAST trial [29], most patients (n = 16/20) had NSCLC and received durvalumab as 1st-3rd line therapy. All of these patients were on ART and had undetectable viral loads, meaning that their HIV infection was controlled and adequately treated, which follows ASCO recommendations regarding the inclusion of PLWH in cancer trials [49]. When putting in perspective the results of the IFCT-1602 CHIVA2 and DURVAST trials [25,29] while looking to the CheckMate 017 and 057 trials [50,51], which evaluated second-line therapy with nivolumab vs docetaxel after platinum-based chemotherapy among patients with squamous and non-squamous NSCLC, respectively, we see that efficacy results were similar. ORR was 13 % and 36 % in the CHIVA2 and DURVAST trials, respectively, while it was 20 % and 19 % in the CheckMate trials. Median OS was 10.9 (2.2-not reached) in the CHIVA2 trial vs 9.2 (95 % CI 7.3–13.3) and 12.2 months (95 % CI, 9.7–15.1) in the CheckMate 017&057 trials. In the retrospective study by Spano [27], evaluating immunotherapy among 21 PLWH, median OS was 10.7 months, in line with the results from the CHIVA2 trial.

Most notably, immunotherapy was safe, with a toxicity profile similar to the HIV non-infected population. The proportion of PLWH experiencing irAEs of any-grade varied from 43 % to 75 % in the pro- spective trials [25,28,29], mostly consisting of grade 1–2 toxicity, which is again similar with the CheckMate 017&057 trials – 58 % and 69 %, respectively [50,51]. Also important, there was no HIV-viral load rebound and no decrease on CD4 + cell counts. Interestingly, in the retrospective study by Chang et al, most patients (n = 7/10) even experienced increases in these CD4 + cell counts while receiving nivo- lumab [24].

5. Limitations

This systematic review has several limitations. Given that most of the included studies were observational and retrospective, there was a high heterogeneity of patient population, with many studies "mixing" pa- tients with NSCLC with those with SCLC or other tumor types, with no separate reporting for some of the efficacy/toxicity variables. Efficacy and safety were also shown for multiple treatment regimens (variable doses of radiotherapy, several chemotherapy schemes…), with no detailed data for each treatment, precluding the performance of a *meta*- analysis.

Moreover, in some older studies, toxicity grading and/or relation of toxicity to treatment was not clear – e.g. the pre-ART study by Peyrade et

al [22], in which five out of seven patients died of sepsis, but where it is not clear if this was directly related to chemotherapy toxicity (i.e. neutropenia) or not.

All included studies were conducted in the US, Japan and Western Europe, preventing the generalization of these data to other world re- gions, especially for Africa, where incidence of lung cancer is expected to increase in the next years [52] and that is home to two-thirds of the people living globally with HIV (a total of 25.7 million people in 2018) [53].

Finally, immunotherapy studies included a heterogeneous popula- tion of patients, receiving these agents as first- to third-line (or more) for advanced disease, while immunotherapy is now recommended as a first- line treatment for NSCLC, where it is considered to be most effective [10]. Thus, these studies no longer apply to the current clinical practice. Moreover, there was limited data on PD-L1 status and on efficacy ac- cording to it, making it difficult to assess the predictive value of this biomarker among PLWH.

5.1. Implications for research & practice

Ongoing and past immunotherapy trials have excluded PLWH. The rationale behind this exclusion is that the extent and type of response mounted by the immune system to lung cancer in these patients is mostly unknown and, therefore, there is a concern that response to immunotherapy may be suboptimal compared to HIV non-infected pa- tients. Yet, pre-clinical studies in PLWH patients with NSCLC [54], anal cancer [55] and head&neck cancer [56] revealed no dramatic differ- ences in tumors' immune infiltrate between HIV-infected vs HIV- uninfected patients. Curiously, in the case-control study with NSCLC patients [54], immune-cell infiltration was more pronounced in tumors from PLWH: there was a higher amount of $CD8^+$ T cells, B cells ($CD20^+$) and macrophages ($CD163^+$). At the same time, HIV infection also in- duces the expression of PD-1 and PD-L1 in immune cells as an escape mechanism, leading to T cell exhaustion [57,58]. Interestingly emerging preclinical and clinical evidence suggest an impact of immunotherapy agents on the host capacity to control HIV infection, highlighting the importance to properly document such use. In a NHP/Rhesus macaque model of chronic SIV infection, blocking PD-L1 with avelumab led to a transient viral control [58]. In humans, there is a report of a patient treated with nivolumab for lung cancer, who had a drastic and sustained decrease of the HIV reservoir paralleling the increase in HIV-specific CD8 + T cells under anti-PD-1 therapy [59]. However, a larger case series including him and another 31 PLWH treated with single-agent anti-PD-1 antibodies for different tumor types showed a very limited impact of these agents on HIV reservoirs and immunity to HIV [60]. This may be due to an immune checkpoints compensatory mechanism, as assessed by the early increase in CTLA-4 and Tim-3 expression. Still, based on this preclinical and clinical evidence, there are two ongoing phase 1 trials testing pembrolizumab in PLWH (without cancer), to assess both its safety and viral/immunologic efficacy (NCT03367754, NCT03239899), which will thus provide more data on its safety in PLWH with cancer. Another approach is the use of chimeric antigen receptor (CAR) *T*-cell therapy, which can work independently of MHC to target HIV-infected cells in order to clear the reservoir (unlike the host's cytotoxic T cells; [61]), and that has shown to be safe in effective in PLWH with hematological malignancies [62]. Thus, there is a biological rationale to use immunotherapy for PLWH with NSCLC and this sys- tematic review adds to it, by showing its effectiveness and safety among those with a controlled infection. Still, more data is needed in the long- term effectiveness and safety of single-agent immunotherapy, immu- notherapy combinations (e.g. anti-PD-(L)1/CTLA4, anti-PD-(L)1/TIGIT or anti-PD-(L)1/CD73 regimens) and chemo-immunotherapy for the treatment of PLWH with NSCLC, both in the early and in the advanced setting. The Empower-Lung 1 trial [63], assessing cemiplimab as 1st-line treatment of advanced NSCLC with PD-L1 ≥ 50 % and the CheckMate 817 trial [64], evaluating nivolumab plus ipililumab, permitted the

enrollment of people with controlled HIV infection. Still, results in this specific subgroup of patients are awaited. All of this knowledge is especially important now that immunotherapy is also being used for stage III NSCLC after chemo-radiotherapy and has been recently approved as (neo)adjuvant therapy for patients with resectable tumors. Moreover, an understanding of NSCLC microenvironment and ge- nomics in PLWH is needed, as this will be paramount to the tailoring of their cancer care and inclusion in future drug trials. Hence, we suggest that future studies should perform a comprehensive assessment of the lung tumor microenvironment in PLWH and compare it to HIV-negative patients, using multiple –omics analyses, such as multiplexed immuno- fluorescence to evaluate the proportion of the different immune subsets in the tumor microenvironment, as well as functional studies to under- stand if the lymphocytes (and other immune cells) around the tumor have the same cytotoxic capacities as the lymphocytes in HIV-negative tumors, among other analyses. This thorough understanding of the tumor immune microenvironment in PLWH could lead to the validation and discovery of predictive biomarkers for immunotherapy efficacy, such as PD-L1 or others, which is also required in this population [65]. As in this systematic review we demonstrate that radiotherapy and systemic therapy are usually safe and effective among PLWH, we hope to raise awareness and persuade healthcare professionals around the world to provide these patients with a similar care to the one given to HIV- negative patients, namely in terms of access to effective treatment and adequate follow-up. This underserved population should be the focus of more research efforts. Thus, PLWH who are on ART and have unde- tectable viral loads should be enrolled in clinical trials testing new anti- cancer therapies [49], such as immune checkpoint inhibitors, as a way to assess the safety and efficacy of innovative treatments in this population. This is paramount in order to reduce the survival gap previously re- ported [4].

6. Conclusions

This systematic review shows that radiotherapy and systemic ther- apy are effective and safe among PLWH diagnosed with NSCLC. None- theless, most reports were small and heterogeneous and larger studies are needed to confirm these encouraging findings. Moreover, clinical trials should not restrict the inclusion of PLWH with controlled infec- tion, as more data is needed regarding the long-term efficacy and safety of treatments, especially of immunotherapy.

Declaration of Competing Interest

MB: travel grant from Roche and Takeda; speaker honoraria from Roche and Janssen; advisory board participation for Sanofi. ND: speaker honoraria from Boerhinger-Ingelheim; advisory board participation for Roche therapeutics; travel grant from MSD. SA: membership on an advisory board or board of directors: MSD, Sanofi, Roche, BMS, Pfizer. NGL: travel grant from Philips; speaker honoraria from AstraZeneca, IPSEN, FERRING.

The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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