Review Article

Use of adjuvant chemotherapy in resected non-small cell lung cancer in real-life practice: a systematic review of literature

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Background: Adjuvant chemotherapy (AC) is recommended since 2004 for patients with a completely resected non-small cell lung cancer (NSCLC). Indeed, several randomized clinical trials have demonstrated an improved survival for patients treated with adjuvant cisplatin-based regimen than surgery alone. In these large clinical trials, patients were well selected and fit to receive AC. As the benefit of AC was estimated at 5.4% of 5-year overall survival (OS), it seems important to evaluate AC use in a less selected population. In particular, elderly patients were underrepresented in large randomized clinical trials. Furthermore, other confounding factors might limit AC efficacy in real-life practice such as the delay of chemotherapy initiation following lung surgery or the number of AC cycles received. Therefore, the aim of this systematic review is to summarize the state of the literature on AC use in current clinical practice.

Methods: A systematic assessment of literature articles and reviews on AC use in real-life practice was performed by searching in several relevant database including Medline, Google Scholar and Cochrane Library following PICOS (i.e., Population, Intervention, Comparison, Outcomes, Study design) eligibility criteria and PRISMA guidelines. Among the 1,957 results obtained with the request formulated on these research database, 56 relevant articles on AC use in non-trial setting were selected and included in the results section.

Results: This systematic literature review highlights the lack of literature on AC use in real-life practice as most of these studies were retrospective. Interestingly, a delayed AC—mostly due to postoperative complications—was better than surgery alone. Furthermore, AC was less purposed to elderly patients, despite retrospective studies outlined that this therapeutic option could be benefit in this specific population as for younger patients. In real-life practice, AC was also often incomplete due to adverse events, but dose reduction or omission was not always associated with an inferior survival. In non-trial setting, number of AC cycles delivered, dose reduction or omission is quite similar to randomized clinical trials.

Discussion: Nowadays, AC is part of the therapeutic strategy used in completely resected NSCLC. In a population of less selected patients, this systematic literature review shows that AC can be used safely and efficiently, especially in elderly patients. As well, delayed AC seems effective. Finally, the place of immunotherapy and targeted therapies have to be precised in the future as well as biomarkers to better select patients that would response to chemotherapy.

Keywords: Adjuvant chemotherapy (AC); non-small cell lung cancer (NSCLC); stage IIA to IIIA; 8th TNM classification

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Introduction

According to 2018 Global Cancer Observatory (GLOBOCAN), lung cancer represents 11.6% of the number of new cases of cancer worldwide and is responsible of 18.4% number of deaths from cancer (1). Adjuvant chemotherapy (AC) for completely resected non-small cell lung cancer (NSCLC) has been implemented at the beginning of the 2000s.

Several randomized clinical trials conducted at the beginning of 2000 have demonstrated an improved survival for patients treated with cisplatin-based AC after complete surgical resection for stage IIA–IIIA NSCLC compared to surgery alone (2-4). The IALT trial (The International Adjuvant Lung Cancer Trial Collaborative Group) was the first and the largest AC trial which demonstrated a statistically significant improvement in overall survival (OS) for patients treated with cisplatin-based AC. Indeed, in the IALT trial which compared cisplatin-based regimen (with etoposide, vinorelbine, vinblastine or vindesine) with surgery alone, the 5-year survival rates were 44.5% and 40.4% (P<0.03) in respectively AC and surgery alone group (*Table 1*) (2). Likewise, JBR.10. (National Cancer Institute of Canada Clinical Trials Group and North American Intergroup Study JBR.10) and ANITA (Adjuvant Navelbine International Trialist Association) clinical trials which compared cisplatin-vinorelbine with surgery alone, demonstrated a significant benefit of AC use on OS (*Table 1*) (3,4). The LACE meta-analysis (Lung Adjuvant Cisplatin Evaluation) included a total of 4,584 patients from five cisplatin-based adjuvant trials (i.e., IALT, JBR.10., ANITA, ALPI-EORTC and Big Lung Trial) (5). This meta-analysis confirmed the benefit of AC with a 5.4% improvement in survival at 5 years (P=0.0043) (*Table 1*). The disease-free survival (DFS) was also significantly improved with a hazard ratio of 0.8 [HR (95% CI): 0.8 (0.78–0.9); P<0.001] (5). Finally, a Cochrane review published in 2015, based on 8,447 individual data analyses showed a benefit of AC with an absolute increase in survival (4% at 5 years) (6). Other clinical trials were conducted but failed to demonstrate a survival benefit of AC. This was the case of the ALPI trial (Adjuvant Lung Project Italy) in which patients received three cycles of mitomycin, vindesine and cisplatin (7). Similarly, the Big Lung Trial showed no benefit of cisplatin-based AC probably due to a lack of patients (8). Furthermore, the CALGB trial (Cancer and Leukemia Group B) which enrolled only patients with IB (i.e., T2N0M0) resected NSCLC failed to demonstrate a statistically significant benefit of Carboplatin-Paclitaxel AC (9). The mortality rate due to AC was estimated at 0.8% of the patients in the IALT (2) and JBR.10. (3) trials whereas it was about 2% in the ANITA trial (4). In the LACE meta-analysis, there were 19 chemotherapy-related deaths reported, corresponding to a 0.9% mortality rate (5) (*Table 1*).

Consequently, since these randomized clinical trials were published, AC is recommended in resected NSCLC for stage IIA to IIIA, according to the 8th TNM classification (10-12). Of note, four cycles of cisplatin-vinorelbine (cisplatin 80 mg/m^2 J1 and vinorelbine 30 mg/m^2 J1–J8) must be preferred. Indeed, in the LACE meta-analysis, the effect of cisplatin-vinorelbine was better in terms of OS and DFS compared to other drugs combination (P=0.11 for OS and P=0.07 for DFS) (5).

In view of contradictory data, the aim of this systematic literature review is to summarize the state of literature regarding AC use in current clinical practice. Indeed, in randomized clinical trials, patients were well selected to fit chemotherapy. In the setting of real-life practice, elderly patients were not included in those clinical trials and chemotherapy was administered in a delay which did not exceed 60 days after surgery. Therefore, as AC provides a moderate benefit of 5.4% of 5-year OS in large randomized clinical trials (5), the assessment of AC efficacy and safety profile in a less selected and more heterogeneous population is valuable. In this context, real-world evidence (RWE) would be interesting to validate whether AC provides same efficacy and safety profile as reported in large randomized clinical trials. Thus, this systematic literature review will detail the use of AC for resected NSCLC in routine clinical practice. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-557).

Materials and methods

A systematic assessment of literature articles and reviews was performed by searching in several relevant database including Medline, Google Scholar and Cochrane Library, following PRISMA guidelines and PICOS (i.e., Population, Intervention, Comparison, Outcomes, Study design) eligibility criteria.

The request formulated in MEDLINE was built in the following way ("Carcinoma, non- small cell lung [MeSH Terms]" OR "resected non-small cell lung cancer [Other Terms]" OR "lung cancer [MeSH Terms]" and "adjuvant

Table 1 Dose intensity, toxicity and OS of main AC randomized clinical trials

Clinical trial	Number of patients included	Stage eligibility	Chemotherapy regimen	Cisplatin-dose intensity	Number of patients completed ≥3 cycles of AC	Neutropenia (grade 3–4)*	AC* related death	OS at 5 years (chemotherapy group)	OS at 5 years (control group)	P value (OS)
IALT (2)	1,867; 932 patients assigned to AC group	I–III	Cisplatin-based (with vindesine, vinorelbine, vinblastine or etoposide)	73.8% received ≥240 mg/m^2	–	17.5%	0.8%	44.5%	40.4%	<0.03
ANITA (4)	840; 348 patients received AC	I–IIIA	Cisplatin-vinorelbine	63% received ≥66% of the total planned dose of cisplatin (i.e., 400 mg/m^2)	61%	76%	2%	51.2%	42.6%	0.017
JBR.10. (3)	482; 242 patients assigned to AC group	IB–II	Cisplatin-vinorelbine	–	58%	73%	0.8%	69%	54%	0.03
LACE meta-analysis (5)	4,584	I–III	–	59% received at least 240 mg/m^2 of cisplatin	–	9% grade 3; 28% grade 4	0.9%	48.8%	43.5%	0.004

*, according to CTCAE classification. CTCAE, Common Terminology Criteria for Adverse Events; OS, overall survival; AC, adjuvant chemotherapy.

chemotherapy [MeSH Terms]" OR "delayed adjuvant chemotherapy [Other Terms]" OR "initiation of adjuvant chemotherapy [Other Terms]"). Applying this request formulation in Medline on 8th March 2021 resulted in 3,137 results. Additional filters were applied ("years of publication from 2004 to 2021"; "language: English"; "abstracts available"; "subject: cancer"; "species: humans") which led to 1692 results. The request formulated in Cochrane Library on 29th September 2021 was built in the following way ("non-small cell lung cancer" [Title, abstract, keyword] AND "adjuvant chemotherapy" [Title, abstract, keyword] AND "observational" [Abstract]) which led to 244 results. Applying this request formulation with additional filters on years of publication (i.e., 2004 to 2021) led to 210 results. The request formulated in Google Scholar on 30th September 2021 was built in the following way ("adjuvant chemotherapy" AND "lung cancer" AND "real-life practice") and allowed to identify 65 results. Additional filter applied based on years of publication (i.e., 2004 to 2021) led to 55 results.

Relevant articles were selected after reading titles and abstracts by one author based on PICOS eligibility criteria (*Table 2*). After screening, eligible articles were either included or excluded through full-text reading by one author. The formulation request, the selection process and the eligibility of articles were critically peer-reviewed by all authors. This research allowed to select 56 relevant articles included in the results section (*Figure 1*).

Results

A total of 1957 titles/abstracts were screened given the search and restriction filters applied on Medline, Cochrane Library and Google Scholar database (*Figure 1*). This preliminary screening restricted our search to 112 potentially eligible papers that were either included or excluded through full-text reading. Overall, 56 relevant articles were selected and included in this systematic literature review (*Figure 1*).

Adherence to guidelines regarding AC administration was estimated at 59% among 99 eligible patients who underwent curative-intent lung surgery for stage II–III NSCLC disease (13) while it was reported at 54.1% among a cohort of 14,892 patients who underwent surgical resection for pN1 disease (14). Barni *et al.* reported the main reasons for no respect to guidelines: patient's refusal (10%), patient's clinical conditions (43%); negative lymph node disease (17%) and clinician's choices (13%) (13).

Table 2 Eligibility criteria for study selection process according to PICOS guidelines

PICOS guidelines	Eligibility criteria	Exclusion criteria
Patients	Patients that underwent curative-intent lung surgery for NSCLC. Patients with theoretical indication of AC or patients who received AC	Patients with advanced or metastatic NSCLC were excluded
		Articles that enrolled only patients with stage I NSCLC disease were excluded
		Patients with other histologic sub-types (i.e., small-cell lung cancer, large cell neuroendocrine lung carcinoma, carcinoid tumours, malignant pleural mesothelioma and other cancers) were excluded
Intervention	AC in real-life practice	Neoadjuvant strategies and other adjuvant strategies (i.e., targeted therapies, immunotherapy, other chemotherapy regimens) were excluded
		Other studies dealing with treatments part of the multimodal strategy (i.e., surgery, radiotherapy, concomitant or sequential chemotherapy) were excluded
Comparison	No control group defined for intervention	–
Outcomes	No primary or secondary endpoints were defined	–
Study design	Prospective or retrospective observational studies on AC use in real-life practice for resected NSCLC. As the first randomized clinical trial on AC was published in 2004, study eligibility criteria also included period of publications from 2004 to 2021	Randomized clinical trials and sub-group analysis on AC out of the context of real-life practice were excluded
		Reviews and meta-analysis about lung cancer and AC out of the context of real-life practice were excluded
		Articles dealing with predictive and prognostic markers in lung cancer, pre-clinical studies, guidelines and case report on lung cancer were excluded

NSCLC, non-small cell lung cancer; AC, adjuvant chemotherapy.

In particular, concerns for AC toxicity was involved in 31% of patient's refusal (15). Consistently with previous observations, advanced age and disease progression were associated with a lower likelihood to receive AC, in 6% cases respectively (16,17). Postoperative complications (18-20) and prolonged length of stay after surgery (21) were also identified as main factors to not receive AC although recommended. In this context, AC use in non-trial setting will be described in the following sections according to the 56 relevant articles selected (*Figure 1*) through the selection process.

Delay of initiation of AC in real-life practice and impact on survival

Several barriers may impact the use of AC in non-trial setting such as patient's decision, physician and patient opinions regarding the ability to tolerate AC and the potential benefits outweigh the risks. As well, recovery from lung surgery and post-operative complications or prolonged length of stay in hospital might contribute to the decision and to delayed AC administration. Notably, referral to medical oncologist is also important to consider in real-life practice.

An observational study reporting patient's and physician's preferences regarding AC, using the time trade-off method, highlighted that most patients and physicians judged moderate survival benefits sufficient to make AC worthwhile after curative-intent lung surgery for a NSCLC (22). As well, the authors described patients' opinions at baseline regarding AC tolerance. Interestingly, the main symptoms expected at baseline by patients were asthenia, nausea, trouble sleeping or lack of appetite whereas main symptoms experienced at 6 months by patients were asthenia, altered sense of taste, constipation or lack of appetite (22). In clinical setting, such symptoms related to AC need to be clearly explained as they might contribute to patient's refusal to underwent AC. In line with these observations, referral to medical oncologist is of particular interest. Of note, preferred and perceived decision making roles on AC were reported as collaborative for both physicians and patients (23). Younis *et al.* reported that 73% patients with stage II–III NSCLC were referred to a medical oncologist (24). Consistently, referral to medical oncologist

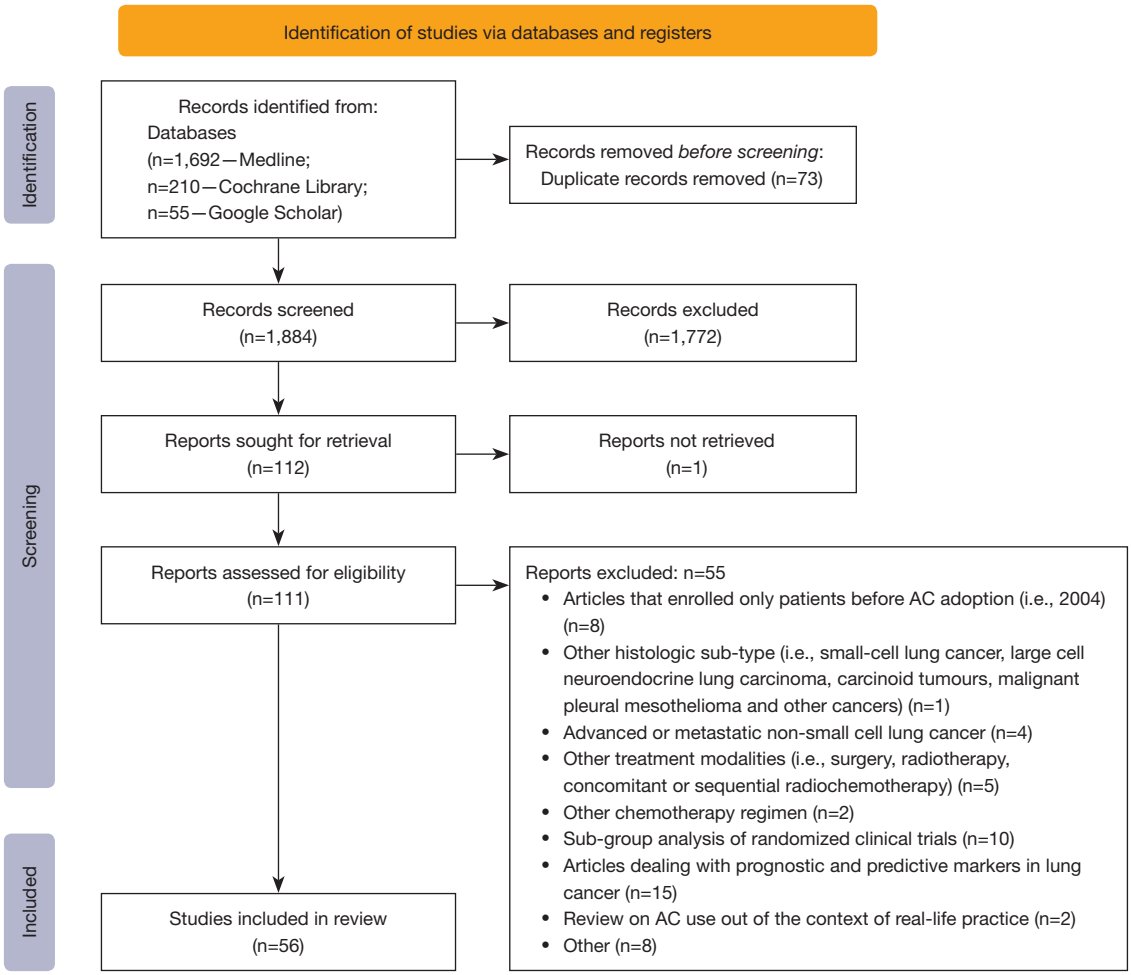

Figure 1 PRISMA 2020 flow diagram presenting the selection process for relevant articles on use of AC in real-life practice. AC, adjuvant chemotherapy.

was reported as 72% among 352 patients with stage IB–IIB NSCLC (15). In another retrospective study, 44% of patients who underwent curative-intent surgery for stage I–III NSCLC were referred to medical oncologist, with a median of 29 days between surgery to medical oncologist referral (25). As well, timeline was estimated at 16 days between medical oncologist referral and consultation and 7 days between medical oncologist's consultation and AC administration (25). A shorter timeline for medical oncologist referral was significantly associated with surgeon requesting for medical oncologist referral (P=0.008) and presence of comorbidities (P=0.036) (25). In multivariate analysis, higher likelihood of referral to medical oncologist was associated with higher stage disease (i.e., stage II/III *vs.* I), surgery (i.e., pneumonectomy) and age (i.e., younger) (24).

Of note, patient's refusal was involved in 5% cases of no referral to medical oncologist (24) while it was estimated at 18% (16) and 2% (26) in other retrospective studies. Apart from patient's refusal (16,24,26), comorbidities, advanced age, postoperative complications and poor performance status (PS) were the main reason advanced by surgeons for judging patients as not fit to receive AC (16,27). Likewise, altered condition after surgery was involved in 7.2% of cases for not referred to medical oncologist (26). Consistently with predictive factors associated with referral to medical oncologist (27), intermediate or high grade tumour (i.e., *vs.* low grade tumour) and higher stage disease (i.e., IIIA *vs.* IIA and IIB) were associated with a higher likelihood to receive AC while advanced aged, pneumonectomy, squamous cell histologic sub-type, higher

Table 3 Median length of stay in hospital after curative-intent lung surgery in non-trial setting

Study	Number of patients included	Period of recruitment	Length of stay in hospital after surgery
Wright *et al.*, 2008, (30)	4,979	Retrospective (2002 → 2006)	Median length of stay: 6 days
			Prolonged length of stay (i.e., exceeding 14 days) for 351 patients (i.e., 7% of patients) with a mean prolonged length of stay of 25.7 days
Massard *et al.*, 2009, (18)	219	Retrospective (2004 → 2005)	Median length of stay: 8 days (range from 2 to 85 days)
Salazar *et al.*, 2017, (32)	12,473	Retrospective (2004 → 2012)	Length of stay ≤14 days: 11,965 patients
			Length of stay exceeding 14 days: 508 patients
Rodriguez *et al.*, 2012, (33)	99	Retrospective (2006 → 2010)	Median length of stay significantly prolonged for patients ≥70 years old (4 *vs.* 6 days for respectively patients <70 and ≥70 years old); P=0.03
			Median length of stay in intensive care unit significantly prolonged for patients ≥70 years old (2.5 *vs.* 1 day for respectively patients <70 and ≥70 years old); P=0.01
Lee *et al.*, 2011, (34)	148	Retrospective (2000 → 2009)	Median length of stay in hospital: 7.05±2.69 days in thoracoscopic lobectomy group *vs.* 8.04±3.39 days in thoracotomy group
			Median stay in intensive care unit: 0.74±0.57 days in thoracoscopic lobectomy group *vs.* 0.97±0.37 days in thoracotomy group (P=0.004)
Jiang *et al.*, 2011, (35)	110	Retrospective (2004 → 2010)	Median length of stay 10.8±3.7 days in VATS group *vs.* 12.5±4.8 days in thoracotomy group (P=0.043)
Bouchard *et al.*, 2008, (31)	60	Retrospective (2004 → 2006)	Median length of stay in hospital 9.3±5.4 days
			Median length of stay was significantly shorter compared to patients who did not receive AC (P=0.0008)

VATS, video-assisted thoracic surgery; AC, adjuvant chemotherapy.

comorbidities according to Charlson index and academic hospital (i.e., *vs.* community hospital) were associated with a less likelihood to receive AC (14,28). Of note, histologic sub-type might be associated with a lower likelihood to receive AC as among a cohort of 94 patients who underwent curative-intent lung surgery for stage II–III squamous-cell carcinoma, only 25.5% of them received AC (29).

Prolonged length of stay in hospital after curative-intent lung surgery might contribute to a delayed administration of AC. The median length of stay in hospital was about 6 days in a retrospective study including 4,979 patients (30) while it was estimated at 8 (18) and 9.3 days (31) in two other retrospective cohorts of 219 and 60 patients respectively (18,31) (*Table 3*). In a large retrospective study which enrolled 12473 patients who underwent AC after curative-intent lung resection, length of stay exceeded 14 days for 508 patients (32) (*Table 3*). Moreover, Bouchard *et al.* found that patients who underwent AC had significant shorter length of stay in hospital compared to those who did not receive AC (P=0.0008) (31). In this setting, predictors for prolonged length of stay in hospital have been described. Wright *et al.* observed that patients with prolonged length of stay after lobectomy surgery have much more postoperative events (3.4 *vs.* 1.2 events, P<0.0001) associated with more comorbidities than the others (30). Similarly, postoperative complications were documented in 40% of patients, mainly postoperative infections (i.e., 35 patients among 87 patients who experienced postoperative complications) (18). Although no significant differences in postoperative complications, baseline comorbidities, surgical procedure and histologic sub-type, Rodriguez *et al.* identified age as a significant prognostic factor for prolonged length of stay after lung resection (33). Indeed, patients older than 70 years old had a significant prolonged length of stay in hospital and intensive care unit compared to younger patients (33) (*Table 3*). Finally, these retrospective studies highlighted that patients who underwent thoracotomy had prolonged length of stay in hospital compared to others (34,35) (*Table 3*).

Nowadays, according to guidelines, AC have to be

initiated within 4 to 8 weeks after curative-intent lung surgery (10-12). The median time between surgery and AC was 40 days and 39 days in the IALT trial (2) and the LACE meta-analysis (5) respectively. For 7% of the patients, the delay to initiate AC exceeded 60 days in the IALT trial (2). In non-trial setting, several retrospective studies were interested in the median time from surgery to AC administration (32,34-43). In real-life practice, these retrospective studies showed that the delay of initiation of AC did not differ significantly compared to clinical trials (*Table 4*). Indeed, the median time between surgery and AC administration was approximately comprised between 5 to 8 weeks (32,34-43) (*Table 4*). Moreover, these studies showed that in real-life practice, AC administration might be delayed after 8 weeks following lung surgery (*Table 4*). In this context, predictors of delayed AC have been described (32,36-38). Squamous cell carcinoma, undetermined grade, pneumonectomy resection, extended length of stay in surgery and unplanned 30-day readmission have been identified as significant predictors of delayed initiation of AC (32,36). Zhu *et al.* also identified higher rate of smoking history as a predictor of delayed AC administration (38). On the contrary, increased comorbidity according to Charlson index (36) and advanced age (39) were not associated with delayed AC. Finally, postoperative complications including infections (16%), postoperative recovery of performance status (32%), patient's decision (18%) and referral delay to medical oncologist (16%) were also described as main factors associated with a delayed AC (37). Interestingly, these retrospective studies outlined that delayed AC was not associated with an increased mortality risk (32,36,38) (*Table 4*). Notably, patients who received delayed AC (i.e., after 57 days) had a lower mortality risk [HR (95% CI): 0.664 (0.623–0.707); P<0.001] compared to patients treated with surgery alone (32). However, patients who received AC >8 weeks after lung surgery have significant shorter OS compared to those who received AC within 8 weeks after lung resection (44). Finally, in accordance with hospital length stay after surgery, thoracotomy surgery is associated with a longer delay of AC administration compared to video-assisted thoracoscopic surgery (VATS) (42) (*Table 4*).

Overall, these retrospective studies highlighted that decision of AC administration is influenced by several predictors including patient's and physician's decision, patient's baseline characteristics, lung surgery and post-operative complications as well as referral to medical oncologist. Although no difference with main randomized clinical trials, all these predictive factors might also contribute with prolonged length of stay in hospital following surgery and thus, delayed AC administration. Otherwise, these retrospective studies outlined that although delayed; AC administration remains associated with a better prognosis compared to surgery alone.

Is age a limiting factor to receive AC in real-life practice?

Despite literature supporting AC use in completely resected IIA to IIIA NSCLC, there is actually a lack of literature data regarding AC use in elderly patients. Indeed, in main randomized clinical trials of AC in NSCLC, elderly patients did not meet the inclusion criteria. Of note, in IALT trial, there were only 4 patients older than 75 years old among 932 patients who received AC (2). In the ANITA trial, the median age in chemotherapy group was 59 years old, with no patients older than 75 years old included (4). Notably, sub-group analysis was conducted based on JBR.10. trial patients' cohort as the age varies from 35 to 82 years old in the chemotherapy group (3,45). Pepe *et al.* analysed the population study of the JBR.10. trial by separating the population study into two groups

Table 4 Time from surgery to AC administration and impact on survival in real-life practice

Study	Number of patients received AC	Period of recruitment	Median time from surgery to AC administration	Impact of delayed AC on survival
Salazar *et al.*, 2017, (32)	12,473	Retrospective (2004 → 2012)	48 (range, 18–127) days	Lower mortality risk when AC initiated in the 50 days after lung surgery (95% CI: 39–56) No increased of mortality risk for patients who received AC later (i.e., between 57 to 127 days after resection): HR (95% CI): 1.037 (0.972–1.105); P=0.27

Table 4 *(continued)*

Table 4 *(continued)*

Study	Number of patients received AC	Period of recruitment	Median time from surgery to AC administration	Impact of delayed AC on survival
Booth *et al.*, 2013, (36)	1,032	Retrospective (2004 → 2006)	8 (range, 1–16) weeks 35% cases initiated AC more than 10 weeks after surgery	No difference observed in 4-year OS between patients who started AC from 1 to 10 weeks after lung resection with those who received delayed AC from 11 to 16 weeks after surgery (64% *vs.* 61%; P=0.758)
Ramsden *et al.*, 2015, (37)	158	Retrospective (2005 → 2010)	8 (range, 3.7–20.3) weeks 24% cases initiated AC more than 10 weeks after surgery	–
Zhu *et al.*, 2016, (38)	409	Retrospective (2003 → 2013)	81.9% patients underwent postoperative AC within 46 days: median 34 (range, 25–45) days 18.1% patients underwent postoperative AC in more than 46 days: median 53.5 (range, 46–228) days	No significant difference in terms of DFS between patients receiving AC either within 46 days after surgery {median DFS [95% CI]: 467 [450–552] days} or after 46 days from surgery {median DFS [95% CI]: 474 [400–623] days}; P=0.775
Zhai *et al.*, 2016, (39)	865	Retrospective (2001 → 2013)	62% of patients received AC between 4 to 6 weeks after surgery	–
Velcheti *et al.*, 2007, (40)	40	Retrospective (2003 → 2005)	49 (range, 16–188) days	–
Lee *et al.*, 2011, (34)	148	Retrospective (2000 → 2009)	28.1±10.7 days in thoracotomy group 26.9±7.5 days in thoracoscopic lobectomy group	–
Jiang *et al.*, 2011, (35)	110	Retrospective (2004 → 2010)	33.7±10.9 days in VATS group 34±13.3 days in thoracotomy group	–
Sorensen *et al.*, 2015, (41)	126	Retrospective (2005 → 2012)	Mean time: 41 days	–
Teh *et al.*, 2014, (42)	44	Retrospective (2008 → 2013)	55.7±3.1 days in VATS resection group *vs.* 68.2±4.3 days in thoracotomy group (P=0.046)	–
Shukuya *et al.*, 2009, (43)	25	Retrospective (2005 → 2008)	Median time from surgery to AC: 41 (range, 29–79) days	–
Wang *et al.*, 2016, (44)	1,522	Retrospective (2004 → 2010)	10% patients received AC <30 days after surgery 17.1% received AC between 0–45 days after surgery 19.05% received AC between 45–60 days after surgery 53.7% received AC >60 days after surgery	Patients who received AC >60 days after surgery have a shorter OS compared to other patients who received AC <60 days after surgery (P=0.0034)

AC, adjuvant chemotherapy; OS, overall survival; DFS, disease-free survival; VATS, video-assisted thoracic surgery.

according to the age (i.e., patients younger or older than 65 years old) (45). Although a potential bias of well selected aged patients, this sub-group analysis outlined that AC can be used safely in elderly patients. Indeed, no significant differences were reported between age groups in terms of chemotherapy toxicities, rate of hospitalization and treatment-related death (45). Moreover, this sub-group analysis highlighted that unless elderly patients received lower intensities of cisplatin-vinorelbine, AC use remained a significant prognostic factor of prolonged OS for patients older than 65 years old [adjusted HR (95% CI): 0.61 (0.38–0.98); P=0.04] compared to surgery alone (45). Likewise, the sub-group analysis of the LACE meta-analysis according to the age (i.e., <65, 65–70, and >70 years old) revealed no significant differences of AC related toxicities (46). As well, the oldest patients received lower doses of cisplatin and lower number of AC cycles. Indeed, only 42% of the elderly patients received a total cisplatin dose ≥275 mg/m^2 in comparison with 64% of young patients (P<0.0001) and; 58% of the elderly patients received more than two or three of the four planned chemotherapy cycles, compared with 77% of young patients (46).

In non-trial setting, several retrospective studies outlined that older patients received significantly less AC compared to their younger counterparts. Indeed, AC use for patients older than 70 years old ranged from 10% to 25% (33,47-51) (*Table 5*). This might be related to a less referral to medical oncologist (52). Otherwise, older patients have a higher likelihood to receive AC in case of higher stage disease, as 42% of patients older than 70 years old with stage IIIA disease were treated with AC (51). Moreover, most of these retrospective studies highlighted that there was no significant difference in chemotherapy regimen received (39,48,54,55) (*Table 5*). Among these, only two studies reported that elderly patients received more frequently Carboplatin-based (P<0.0001) (49) or Carboplatin-paclitaxel regimen compared to younger (without a statistical significance) (55) (*Table 5*).

In real-life practice, despite contradictory data (33), no significant differences in the number of chemotherapy cycles received was observed between younger and older patients (39,54). Of note, the percentage of patients older than 65 years old who completed four cycles of AC ranged from 61% (50) to 92.4% (39,54,55) (*Table 5*). Likewise, no significant differences in terms of dose intensity received was reported (55). A dose reduction was reported among 30% (48) to 40.9% (55) of older patients while a dose omission was observed between 21% to 32% of cases (48) (*Table 5*). As an assessment of well-tolerated AC in this specific population, no significant difference was reported between patients younger and older than 65 years old regarding hematologic toxicities, except for all grade anemia (55). Notably, grade 3–4 neutropenia was not significantly more frequent in older patients (i.e., 39.4%) compared to their younger counterparts (i.e., 41.1%) (55). Adverse events reported by elderly patients during AC treatment were sore mouth (P=0.0032), peripheral neuropathy (P<0.001) and alopecia (P<0.001) (55). Overall, quality of life (QOL) during AC treatment did not significantly deteriorate among elderly patients (55).

More interestingly, several studies outlined that AC is efficient in this sub-population (39,49-51,53-55) (*Table 5*). Indeed, AC significantly improved OS compared to surgery alone among patients older than 66 (49) or 70 years old (51,53). As well, no significant differences were reported between younger and older patients who received AC in terms of OS (49-51,53-55) and DFS (39,54,55) (*Table 5*). However, Wisnivesky *et al.* observed that AC use was not associated with a survival benefit for patients older than 80 years old (53).

Overall, these retrospective studies showed that unless AC is used less frequently among elderly patients, AC remains safe and efficient in non-trial setting. As for their younger counterparts, fit older patients should be treated with platinum based chemotherapy; cisplatin remained preferrable if patient suitable to receive it (56). As an exception, AC use might be carefully discussed for patients older than 80 years old as no survival benefit was observed (53,57). Otherwise, chronological age should not be considered as a limiting factor to receive AC as well as performance status (57). Indeed, several reviews on AC use in clinical practice among elderly patients, outlined that comprehensive geriatric assessment is of particular interest to limit both over and undertreatment in this specific population (56-61).

Which type of chemotherapy is used in real-life practice? Are patients received the planned dose of AC?

AC, and in particular cisplatin-based regimen, may have toxicity. Consequently, this arises the question of patients who subsequently received AC when recommended as well as the regimen and dose intensity received in non-trial setting.

According to main randomized clinical trials, among patients assigned to receive AC, the percentage of patients

Table 5 Use of AC in elderly patients

Study	Number of patients who underwent surgical resection; stage disease	Number of patients received AC	Period of recruitment	AC use in elderly patients	Chemotherapy regimen prescribed	Dose modification or omission	Survival analysis elderly patients
Booth *et al.*, 2010, (47)	3,354; 43% older ≥70 years old; I–IV	1,224	Retrospective (2001 → 2006)	16% of patients >70 years old received AC	Cisplatin or carboplatin-based regimen	–	–
Cuffe *et al.*, 2012, (48)	6,304; 43.8% older ≥70 years old; I–IV	1,224	Retrospective (2001 → 2006)	70–74 years old: 191 patients received AC among 1,317 who underwent lung resection	Cisplatin-based regimen (with vinorelbine or etoposide); carboplatin-based regimen (with vinorelbine or paclitaxel); other	584 chemotherapy data available:	–
				75–79 years old: 81 patients received AC among 980 who underwent lung resection	584 chemotherapy data available:	Cisplatin changed for carboplatin: 5% among 75–79 years old patients	
				≥80 years old: 13 patients received AC among 466 patients who underwent lung resection	Cisplatin-based: 71% (70–74 years old), 67% (75–79 years old), 71% (≥80 years old)	Dose reduction: 30% (70–74 years old), 32% (75–79 years old)	
					Carboplatin-based: 26% (70–74 years old), 33% (75–79 years old), 29% (≥80 years old)	Dose omission: 21% (70–74 years old), 32% (75–79 years old), 25% (≥80 years old)	
Ganti *et al.*, 2015, (49)	7,593; 38% older ≥70 years old; IB–III	1,928	Retrospective (2001 → 2011)	Percentage of older patients (i.e., ≥70 years old) who received AC: approximately one half of younger patients (15.3% *vs.* 31.6%; P<0.0001)	Cisplatin or carboplatin-based regimen Compared with younger patients, patients ≥70 years old received significantly more frequently carboplatin-based regimen (72% *vs.* 62.3%; P<0.0001)	–	As for younger patients, AC significantly improved OS among patients ≥70 years old [adjusted HR (95% CI): 0.81 (0.71–0.92)]
Kankesan *et al.*, 2013, (52)	3,354; 45% older ≥70 years old; I–IV	1,032	Retrospective (2004 → 2006)	Patients older than 70 years old significantly less referred to medical oncologist (45% of patients; P<0.001)	–	–	–
				Patients older than 70 years old significantly less treated with AC (35% of patients older than 70 years old referred to medical oncologist treated with AC; P<0.001)			

Table 5 *(continued)*

Table 5 *(continued)*

Study	Number of patients who underwent surgical resection; stage disease	Number of patients received AC	Period of recruitment	AC use in elderly patients	Chemotherapy regimen prescribed	Dose modification or omission	Survival analysis elderly patients
Rajaram *et al.*, 2016, (28)	112,049; 20% older ≥75 years old; IB–IIIA	31,709	Retrospective (2002 → 2011)	Compared to patients younger than 55 years old, patients older than 56 years old have significantly less likelihood to receive AC [adjusted OR (95% CI); especially among patients >75 years old: 0.15 (0.12–0.18); P<0.001]	–	–	–
Berry *et al.*, 2015, (50)	2,781 patients >65 years old; stage II	784	Retrospective (1992 → 2006)	Patients aged 70–74, 75–79, 80–84 and ≥85 years old received significantly less AC	Platinum-based regimen administered to 76% of patients	61% received four or more cycles (no information about dose reduction)	AC remained an independent prognostic factor associated with survival among all patients aged ≥66 years old (P=0.0002)
Wisnivesky *et al.*, 2011, (53)	3,324 patients >65 years old; IIA–IIIA	684	Retrospective (1992 → 2005)	–	–	–	AC associated with improved OS for patients 70–79 years old [adjusted HR (95% CI): 0.82 (0.71–0.94)] No survival benefit for patients older than 80 years old [adjusted HR (95% CI): 1.33 (0.86–2.06)]
Rodriguez *et al.*, 2012, (33)	99; 30% ≥70 years old; IB, II and higher	53	Retrospective (2006 → 2011)	Patients ≥70 years old received significantly less AC compared to youngers; (25% *vs.* 66.7%; P<0.01)	–	Significantly less cycles of chemotherapy received for patients aged ≥70 years old (median number of cycles received 2 {range, [1–2]} compared to younger (median number of cycles received 4 {range, [2–4]}; P=0.04	–

Table 5 *(continued)*

Table 5 *(continued)*

Study	Number of patients who underwent surgical resection; stage disease	Number of patients received AC	Period of recruitment	AC use in elderly patients	Chemotherapy regimen prescribed	Dose modification or omission	Survival analysis elderly patients
Batum *et al.*, 2018, (54)	–; IA–IIIB	91	Retrospective (2012 → 2016)	–	Platinum-based regimen with vinorelbine, pemetrexed, gemcitabine, etoposide, docetaxel	No significant differences between number of cycles of AC received	No significant differences between younger and older patients in terms of OS (P=0.119) and DFS (P=0.407)
					>65 years old patients treated with: platinum + vinorelbine (70%); carboplatin-based regimen (5%)	90% of patients >65 years old completed four cycles of AC	
					No significant differences in chemotherapy regimen administered between younger and older patients		
Zhai *et al.*, 2016, (39)	–; IB–IIIA	865	Retrospective (2001 → 2013)	–	Platinum-based regimen with vinorelbine, pemetrexed, gemcitabine, docetaxel, paclitaxel	No significant differences between number of cycles of AC received	No significant differences in DFS between younger and older patients (P=0.328)
					No significant differences in chemotherapy regimen received between younger (i.e., <65 years old) and older patients (i.e., ≥65 years old)	79.1% of patients ≥65 years old completed four cycles of AC	
						No significant differences in mean time to receive AC after surgery between younger and older patients	
Park *et al.*, 2013, (55)	–; IB–IIIA	139	Retrospective (2008 → 2011)	–	Chemotherapy regimen: cisplatin-vinorelbine or carboplatin-paclitaxel	No significant differences in mean dose intensity and relative dose intensity between younger and older patients for both AC regimen	No significant differences between aged groups (i.e., <65 years old and ≥65 years old) in terms of OS (P=0.4274) and relapse-free survival (P=0.4512)
					Elderly patients (66 patients ≥65 years old) most frequently treated with carboplatin-paclitaxel (54.5%) and less frequently with cisplatin-vinorelbine (45.5%) although not significant	92.4% of elderly patients completed 4 cycles of AC	
						40.9% of elderly patients has a dose reduction, no significant difference compared to youngers	

Table 5 *(continued)*

Table 5 *(continued)*

Study	Number of patients who underwent surgical resection; stage disease	Number of patients received AC	Period of recruitment	AC use in elderly patients	Chemotherapy regimen prescribed	Dose modification or omission	Survival analysis elderly patients
Lin *et al.*, 2012, (51)	2,231; 764 patients ≥70 years old; IA–IIIA	428	Retrospective (2004 → 2007)	Among patients ≥70 years old with stage II disease: 16% received AC Among patients ≥70 years old with stage IIIA disease: 42% received AC	Platinum-based regimen	–	Among patients >70 years old with stage II and IIIA disease: AC use associated with a significant improvement of OS compared to surgery alone

AC, adjuvant chemotherapy; OS, overall survival; DFS, disease-free survival.

who never received chemotherapy ranged from 4.5% to 9.8% (2-4); mainly due to patient's refusal. Among patients who received AC, 73.8% received at least 240 mg/m^2 of cisplatin in the IALT trial (2) while 38% and 63% patients received more than 66% of the total planned dose of vinorelbine and cisplatin respectively in ANITA trial (4) (*Table 1*). In the LACE meta-analysis, 59% of patients received at least 240 mg/m^2 of cisplatin (5) (*Table 1*). The median number of cycles delivered was three in the JBR.10. trial (3); 77% of patients had at least one dose reduction or omission and 55% required at least one dose delay (3). Main factors associated with incomplete chemotherapy planned in IALT trial were adverse events (51.5%), patient's or physician's decision (24.3%) and disease progression (5.1%) or early death (8.1%) (2). Similarly to the IALT trial, the main reasons for receiving less than the planned number of AC cycles were patient's refusal (35%), toxicity (34%) and early death or progression (9%) in the LACE meta-analysis (5).

Firstly, these studies highlight that cisplatin-based regimen is the most frequently used in non-trial setting (*Table 6*). Of note, consistently with guidelines, cisplatin-vinorelbine is the most frequently AC regimen prescribed by physicians in real-life practice (*Table 6*). On the contrary, only two retrospective studies mentioned that carboplatin-paclitaxel regimen was the most frequently prescribed AC regimen (24,66). Otherwise, these studies either included patients previously main randomized clinical trials were published (66) or recently published (24) and; the median age of patients was older than 66 years old (66). In this setting, initial chemotherapy regimen was changed for 6% (62) to 8% (63) of patients (i.e., mainly cisplatin for carboplatin-based regimen). The main reasons involved for this chemotherapeutic change were nephrotoxicity, asthenia and vomiting (63). Although heterogeneity data (18,22,41,68,70), the number of patients who completed four cycles of AC ranged from 71% to 92% in non-trial setting (*Table 6*). In particular, the percentage of patients who received the total planned dose ranged from 40% (40) to 78.4% (34). Moreover, patients experience dose reduction or omission in a range of 40% (63) to 64% (62) (*Table 6*). In particular, dose reduction was significantly associated with cisplatin-used (P=0.004) and poorer ECOG (i.e., performance status 0–1 as reference, P=0.020) (37). In line with these observations, cisplatin-vinorelbine regimen was significantly associated with higher frequency of dose delay or dose reduction compared to patients treated with carboplatin-paclitaxel (70). Although dose modification was not found to be associated with inferior survival (62),

Table 6 AC regimen used and dose intensity, AC toxicity in real-life practice

Study	Period of recruitment	Number of patients treated with AC	Chemotherapy regimen prescribed	Dose reduction or omission	All grade 3–4* toxicity reported (% of patients)
Booth *et al.*, 2012, (62)	Retrospective (2004 → 2006)	584	Cisplatin-based regimen (with vinorelbine or etoposide): 82% carboplatin-based regimen (with vinorelbine or paclitaxel): 17%; other (no platinum): 1%	Initial chemotherapy regimen changed: 6% (mainly cisplatin for carboplatin)	–
			Most frequent regimen: cisplatin-vinorelbine (72%)	Among 520 drug dosages available: 56% dose reduction or omission	
				Cisplatin-vinorelbine sub-group: 64% dose reduction or omission	
Ramsden *et al.*, 2015, (37)	Retrospective (2005 → 2010)	158	Cisplatin-vinorelbine: 80%; carboplatin-paclitaxel: 15%; other: 5%	Median number of AC cycles received: 4	–
				72% of patients received >80% of planned dose of cisplatin or carboplatin	
Aljubran *et al.*, 2009, (63)	Retrospective (2003 → 2005)	50	Cisplatin-based regimen (with vinorelbine, gemcitabine or etoposide): 88%; carboplatin-based regimen (with vinorelbine, gemcitabine or paclitaxel): 12%	Initial chemotherapy regimen changed: 8% (cisplatin for carboplatin)	Grade 3–4 neutropenia: 28%; febrile neutropenia: 10%
			Most frequent regimen: cisplatin-vinorelbine (82%)	80% of patients completed 4 cycles of AC	Grade 3–4 anemia (4%) and thrombocytopenia (2%)
				Dose reduction: 40%	Grade 3–4 asthenia: 10%
				Mean dose of cisplatin received: 240.1 mg/m^2	Grade 3–4 anorexia, nausea: 4% respectively
				Mean dose of vinorelbine received: 165.3 mg/m^2	Grade 3–4 vomiting, diarrhea, constipation: 2% respectively
Kenmotsu *et al.*, 2012 and 2017, (64,65)	Retrospective (2006 → 2011)	100	Cisplatin-vinorelbine	83% of patients completed 4 AC cycles	–
				59% of patients received the planned dose (i.e., cisplatin 320 mg/m^2 and vinorelbine 200 mg/m^2)	
				65% of patients received >300 mg/m^2 of cisplatin	
Massard *et al.*, 2009, (18)	Retrospective (2004 → 2005)	87	Cisplatin-based regimen (with vinorelbine, gemcitabine, paclitaxel or etoposide): 58%	40% of patients completed 4 AC cycles	29% patients experienced grade 3–4 toxicities; among them 12% of hematological toxicities and 16% of non-hematological toxicities (nausea/vomiting, acute renal failure and central venous infection)
			Carboplatin-based regimen (with vinorelbine, gemcitabine, paclitaxel or etoposide): 31%		
			Most frequent regimen: cisplatin-gemcitabine (27%)		

Table 6 *(continued)*

Table 6 *(continued)*

Study	Period of recruitment	Number of patients treated with AC	Chemotherapy regimen prescribed	Dose reduction or omission	All grade 3–4* toxicity reported (% of patients)
Williams *et al.*, 2014, (66)	Retrospective (2001 → 2008)	1,084	Cisplatin-based regimen (with vinorelbine, docetaxel, etoposide or other): 29%; carboplatin-based regimen (with docetaxel, gemcitabine, paclitaxel or other): 71%; other (no platinum): 3% Most frequent regimen: carboplatin-paclitaxel (52%)	–	–
Moth *et al.*, 2016, (23)	Prospective (2010 → 2012)	98	Cisplatin-vinorelbine most frequent regimen: 74%	71% of patients completed 4 AC cycles	–
Paull *et al.*, 2006, (67)	Prospective (2004 → 2006)	10	Carboplatin-paclitaxel	Average dose of 1,074±212 mg/m^2 carboplatin and 708±50 mg/m^2 of paclitaxel Average number of AC cycles received 4±0.5	3 cases of grade 1–3 neutropenia or thrombocytopenia reported 2 cases of grade 1–3 gastrointestinal disturbance reported No grade 4 toxicity reported
Park *et al.*, 2013, (55)	Retrospective (2008 → 2011)	139	Cisplatin-vinorelbine: 53.2%; carboplatin-paclitaxel: 46.8%	Dose reduction in the global cohort: 58.3%	In the global cohort: Leukopenia grade ≥3: 9.3% Neutropenia grade ≥3: 40.3% Anemia grade ≥3: 2.9%
Kolek *et al.*, 2018, (19)	Retrospective (2006 → 2013)	115	Platinum-based regimen with vinorelbine or other	82% completed cycles with platinum-based regimen and oral vinorelbine Average number of cycles received: 3.87	Grade 3–4 neutropenia: 34.4% of patients. Febrile neutropenia: 2.2% Grade 3–4 nausea: 33.3%
Velcheti *et al.*, 2007, (40)	Retrospective (2003 → 2005)	40	Cisplatin-docetaxel most frequent regimen: 43% Other AC regimen: carboplatin-paclitaxel (17%), carboplatin-docetaxel (17%); carboplatin-gemcitabine (15%)	40% of patients received the planned dose 53% had AC dose reduction 8% had AC dose delay	42% experienced grade 3–4 toxicities with 25% grade 3–4 neutropenia
Kassam *et al.*, 2007, (16)	Retrospective (2003 → 2005)	42	Cisplatin-vinorelbine most frequent regimen: 67% Other regimen: cisplatin-etoposide, carboplatin-paclitaxel (9.5%), cisplatin-gemcitabine	–	–

Table 6 *(continued)*

Table 6 *(continued)*

Study	Period of recruitment	Number of patients treated with AC	Chemotherapy regimen prescribed	Dose reduction or omission	All grade 3–4* toxicity reported (% of patients)
Blinman *et al.*, 2015, (22)	Prospective	106	Cisplatin-vinorelbine most frequent regimen: 73% Other regimen: platinum + gemcitabine	68% completed 4 AC cycles	–
Younis *et al.*, 2008, (24)	retrospective (2005)	29	Carboplatin-paclitaxel most frequent regimen: 79.3% Cisplatin-vinorelbine (17.2%), carboplatin-vinorelbine (3.4%)	–	–
Chouaid *et al.*, 2018, (20)	Retrospective (2009 → 2011)	402	Cisplatin-vinorelbine most frequent regimen: 64.2% Other regimen: carboplatin-vinorelbine, cisplatin-gemcitabine	Median number of AC cycles received: 4 62.1% completed the total planned dose of cisplatin 66% completed the total planned dose of vinorelbine	–
Couillard-Montminy *et al.*, 2017, (68)	Retrospective (2004 → 2013)	127	Cisplatin-vinorelbine most frequent regimen: 52%; carboplatin-vinorelbine	47% patients completed 4 cycles of cisplatin-vinorelbine	In cisplatin-vinorelbine group: Grade 3–4 neutropenia: 62.1%. Febrile neutropenia: 4.6% Grade 3–4 anemia: 15.2% Blood transfusion support for 25.8% patients
Lee *et al.*, 2011, (34)	Retrospective (2000 → 2009)	148	Cisplatin-based regimen most frequent (no other precision)	89% patients completed 4 cycles of AC 78.4% patients received the total planned dose	–
Jiang *et al.*, 2011, (35)	Retrospective (2004 → 2010)	110	Carboplatin-paclitaxel (40.9%); cisplatin-gemcitabine (49%) and cisplatin-vinorelbine (0.1%)	45.5% patients received the total planned dose	28.2% experienced grade 3–4 toxicity Grade 3–4 neutropenia: 19% Grade 3–4 nausea: 18.2%
Sorensen *et al.*, 2015, (41)	Retrospective (2005 → 2008)	126	Cisplatin-vinorelbine	59% completed 4 cycles of AC 10% patients received one cycle with dose reduction, 6% patients received two cycles with dose reduction, 2% patients received 3 cycles with dose reduction, 6 % patients received four cycles with dose reduction	–

Table 6 *(continued)*

Table 6 *(continued)*

Study	Period of recruitment	Number of patients treated with AC	Chemotherapy regimen prescribed	Dose reduction or omission	All grade 3–4* toxicity reported (% of patients)
Custodio carretero *et al.*, 2008, (69)	Retrospective (2003 → 2006)	41	Carboplatin associated with docetaxel or paclitaxel; cisplatin associated with docetaxel or paclitaxel	56.1% received 4 AC cycles	Grade 3–4 haematological toxicities: 9.75%. 2 patients with febrile neutropenia
				12.2 % patients had a dose reduction and 9.75% had a dose delay	Grade 3–4 non-haematological toxicities: 7.31%
Chang *et al.*, 2014, (70)	Retrospective (2004 → 2011)	438	Carboplatin-paclitaxel (47.3%) and cisplatin-vinorelbine (52.7%)	Median number of AC cycles received: 4 in both groups	Grade 3–4 anemia (P=0.008) and neutropenia (P<0.001) were significantly more frequent in cisplatin-vinorelbine group
				55.1% completed 4 cycles in carboplatin-paclitaxel group	Grade 3–4 neutropenia: 38.1% in cisplatin-vinorelbine group *vs.* 7.2% in carboplatin-paclitaxel group
				50.6% completed 4 cycles in cisplatin-vinorelbine group	Most frequent grade 3–4 AC related toxicities in cisplatin-vinorelbine group: nausea (2.2%), vomiting (2.2%) and constipation (1.7%)
				19.8% in carboplatin-paclitaxel group *vs.* 56.3% in cisplatin-vinorelbine group required a dose delay (P<0.001)	Most frequent grade 3–4 AC related toxicities in carboplatin-paclitaxel group: peripheral neuropathy (2.9%), myalgia (1.9%), alanine aminotransferase and infection (1.0% respectively)
				16.4% of patients in carboplatin-paclitaxel group had a dose reduction *vs.* 35.1% in cisplatin-vinorelbine group (P<0.001)	
				Cumulative dose received: 83% for carboplatin and paclitaxel respectively; 83% and 82% for cisplatin and vinorelbine respectively	
Teh *et al.*, 2014, (42)	Retrospective (2008 → 2013)	44	Platinum with vinorelbine	45% patients completed 4 cycles at 100% of planned dose of platinum-based and vinorelbine	29.5% presented grade 3–4 haematological toxicities
Shukuya *et al.*, 2009, (43)	Retrospective (2005 → 2008)	25	Cisplatin-vinorelbine	92% patients completed 4 AC cycles	76% patients presented grade 3–4 neutropenia. Febrile neutropenia =4%
				Mean cumulative dose of cisplatin was 312 mg/m^2 and 195 mg/m^2 for vinorelbine	20% patients presented grade 3–4 leukopenia
				20% patients had a dose reduction	12% patients presented anemia, anorexia and nausea respectively

Table 6 *(continued)*

Table 6 *(continued)*

Study	Period of recruitment	Number of patients treated with AC	Chemotherapy regimen prescribed	Dose reduction or omission	All grade 3–4* toxicity reported (% of patients)
Bouchard *et al.*, 2008, (31)	Retrospective (2004 2006)	60	Cisplatin-vinorelbine most frequent regimen: 46.9% Other regimen: carboplatin based regimen with paclitaxel, gemcitabine, vinorelbine; cisplatin based regimen with etoposide or gemcitabine	–	Grade 3–4 cytopenia reported in 47.8% patients treated with cisplatin-vinorelbine regimen

*, according to CTCAE classification. AC, adjuvant chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events.

Ramsden *et al.* showed that patients with a delivery of <80% of total planned platinum dose was a significant factor affecting OS (37). Likewise, the number of AC cycles received is important to consider as patients who received four AC cycles had a significant prolonged DFS compared to those who received less than four cycles of AC [HR (95% CI): 0.727 (0.552–0.958); P=0.0023] (39). On the contrary, Kenmotsu *et al.* found that the total dose of cisplatin received was not a prognostic factor (64). Finally, main reasons for discontinuation of AC were AC toxicities (i.e., 8%) and patient's refusal (i.e., 8%) (64,65). Finally, thoracoscopy seems to be associated with higher compliance to AC compared to thoracotomy (34,35). Indeed, a significant higher rate of patients completed 4 AC cycles in case of thoracoscopy compared to thoracotomy (34,35).

Taken together, these studies showed that physicians prescribe mostly cisplatin-vinorelbine regimen. In a population of less-selected patients, literature data showed that the percentage of patients who received either 4 AC cycles or experienced dose reduction or omission is not different compared to randomized clinical trials.

AC related toxicities

Finally, a major point to take into account in real-life practice is the toxicity of AC, which can lead to either dose reduction or omission and incomplete planned dose received. In main randomized clinical trials, the rate of overall grade 3–4 toxicity was estimated at 66% (5). In particular, neutropenia was reported as the most frequent serious adverse event occurring in patients treated with AC: 9% grade 3 and 28% grade 4 neutropenia reported in the LACE meta-analysis while 73% and 76% of patients experienced grade 3 or 4 neutropenia in the JBR.10. and ANITA trials respectively (*Table 1*).

Similar to AC clinical trials, neutropenia remains the most frequent adverse event reported in real-life practice (*Table 6*). In contrast with Shukuya *et al.* (43) who reported 76% of patients experienced grade 3–4 neutropenia, other studies highlight that in non-trial setting neutropenia occurrence is not more frequent compared with randomized clinical trials (*Table 6*). Indeed, the rate of grade 3–4 neutropenia ranged from 19% (35) to 62.1% (68), with up to 10% of patients who experienced febrile neutropenia (63) (*Table 6*). In this setting, neutropenia was significantly more frequent in case of cisplatin-vinorelbine regimen (P<0.001) (70). In real-life practice, other AC adverse events frequently reported were asthenia, anorexia and nausea-

vomiting (*Table 6*). Moreover, AC related toxic death was low in randomized clinical trials with a rate ranging from 0.8% to 2% (*Table 1*). Similar observations were reported according to retrospective studies in real-life practice (18,40,62,64,65,69). Indeed, 0.009% to 1.6% related AC toxicity death were reported by Massard *et al.* (18) and Booth *et al.* (62) respectively, while other retrospective studies reported no AC toxic death (40,64,65,69). In this context, predictors of early mortality (i.e., within 6 months following AC administration) have been identified (71). Prolonged length of stay in hospital (>6 days), 30-day readmission on hospital, higher stage disease, higher comorbidities according to Charlson index (i.e., ≥2) and pneumonectomy were significantly associated with higher risk of early mortality following AC administration (71). Notably, AC related toxic death seems to be more frequent in older patients. Indeed, AC related toxic death within 12 weeks following AC administration was estimated at 3.1% among a population of 684 patients with a mean age of 71.5 years old (53). Moreover, this retrospective study outlined the increased risk of dehydration in this specific population which occurred in 6.7% (53). In accordance with Wisnivesky *et al.*, patients older than 80 years old or aged between 70 and 80 years old were also identified at higher risk of early mortality (i.e., within 6 months following AC administration) compared with younger patients (i.e., <50 years old) (71). The mortality rate at 6 months was 7.6% among patients older than 80 years old (71).

Finally, sub-group analysis of the JBR.10. trial showed that patients had transient worsening QOL scores following AC (72). Otherwise, these scores were found to return to baseline within 9 months following AC, except for sensory neuropathy (72). In non-trial setting, patients also experienced a transient worsening QOL partially associated with AC administration (67). Indeed, Paull *et al.* reported all three measures of global QOL (Trial Outcome Index, Functional Assessment of Cancer Therapy-Lung and Functional Assessment of Cancer Therapy-General) as well as the subscales of physical and functional well-being at baseline and after lung resection among 37 patients for a stage I–III NSCLC disease. These scores were significantly decreased at 0 to 3 months compared with baseline whereas these scores were not significantly different from baseline after 3 months (67).

Overall, consistently with clinical trials, literature data regarding AC toxicity in non-trial setting highlight that AC use is mostly associated with a risk of neutropenia. AC administration remains well-tolerated in most of patients and might be associated with a transient worsening QOL.

Discussion

At the beginning of 2000, AC has been implemented in NSCLC with the aim to reduce the risk of disease recurrence through eliminating residual disease. To our knowledge, this is the first systematic literature review reporting AC use for resected NSCLC patients in real-life practice as previous reviews on this topic focused on AC use in elderly patients. This systematic literature review highlights a lack of literature data regarding AC use in real-life practice, as most of these were retrospective studies. Although data from large registries such as National Cancer Database or SEER (Surveillance, Epidemiology and End Results program) database, most of the retrospective studies included were either monocentric or multicentric with a limited number of patients which might limit external validity of results. Similarly, retrospective studies are also subjected to potential bias, in particular selection bias and information or misclassification bias. As well, although broad search terms were applied in the request formulated on several research database in order not to miss relevant articles, only one author carried out the selection and peer-reviewed process which constitute a potential bias of selection. Otherwise, the eligibility and the relevance of articles selected was peer-reviewed by all authors.

Despite the absence of a control group and the quality of data sources and collection, RWE has gained increased interest recently as they could focus on a specific population underrepresented in randomized clinical trials or provide pharmaco-economic data. There is a lack of RWE regarding AC use in resected NSCLC patients. In this setting, RWE would be interesting to evaluate AC use in elderly patients or in stage IB disease as AC use remains controversial in these specific populations. Notably, in the context of adjuvant immunotherapy and targeted therapies development, RWE on AC would be valuable to define which patients would better benefit from these different therapeutic options in next future and provide pharmaco-economic data.

Consistently with randomized clinical trials, this systematic literature review shows that benefit outweigh the risk is in favour of AC use when recommended. Indeed, in a less-selected population, AC use remains safe and associated with a therapeutic efficacy. In particular, this systematic review highlights that AC could be used in fit elderly patients—especially for those younger than 80 years old—

which is a frequent clinical situation in daily-life practice. Furthermore, delayed AC remains efficient compared to surgery alone.

Nowadays, guidelines for AC administration are mainly based on patient's clinical characteristics (age, performance status) and NSCLC disease's characteristics. In this context, there has been a great interest to identify prognostic and predictive biomarkers of AC treatment to better select patients. However, these interesting markers such as DNA methylation, miRNA or gene signatures have not proven their clinical value in prospective trials yet (73). In this context, other biomarkers currently used in metastatic context tend to be used as well in early-stage NSCLC disease. Thus, the specific place of standard AC has to be precised in the next future since targeted therapies and immunotherapy seem promising strategies in adjuvant setting. Indeed, although the therapeutic efficacy of PD-1 and PD-L1 antibodies remain currently unclear in adjuvant treatment strategies for NSCLC, preliminary results of phase III IMpower010 (NCT02486718) randomized clinical trial hopes for future. Primary results recently reported at ASCO (American Society of Clinical Oncology) meeting 2021 showed that patients who received atezolizumab following AC have significant increased DFS compared to best supportive care (P=0.0395 after a median follow-up of 32.2 months) (74). In the same way, other phase III randomized trials are currently ongoing to evaluate the impact of immune checkpoint inhibitors on DFS following AC treatment (ANVIL trial NCT02595944; PEARLS/Keynote091 trial NCT02504372; BR31 Canadian Cancer Trial Group NCT02273375). In case of oncogenic-driven mutations, ADAURA trial recently demonstrated that osimertinib significantly prolonged DFS after curative-intent lung surgery compared to placebo for patients harbouring *EGFR*-sensitizing mutations (i.e., del19 and L858R EGFR mutations), regardless patients received AC or not (75).

To conclude, despite a lack of literature regarding AC use in real-life practice, this systematic literature review reports that AC use is safe and efficient in non-trial setting. Several strategies are currently under development to better select patients that will benefit from AC and to implement other strategies depending on immune checkpoint inhibitors and targeted therapies.

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Footnote

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