CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2018.1490254
Article RT-0194.R1/1490254

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Real life adjuvant chemotherapy uptake and survival in patients with non-small cell lung cancer after complete resection

Vítězslav Kolek[a], Stanislav Losse[a], Juraj Kultan[a], Petr Jakubec[a], Zatloukal Jaromir[a], Milan Sova[a], Marek Szkorupa[b], Čestmír Neoral[b], Josef Škarda[c], Tomáš Tichý[c] and Zdeněk Kolář[c]

[a]Department of Respiratory Medicine, University Hospital Olomouc, Olomouc, Czech Republic; [b]Department of Surgery, University Hospital Olomouc, Olomouc, Czech Republic; [c]Department of Molecular Pathology, Palacky University, Olomouc, Czech Republic

ABSTRACT

Objectives: Adjuvant chemotherapy (AC) in non-small cell lung cancer (NSCLC) has become a standard of care in patients with stages IIA, IIB, and IIIA after complete tumor resection. Utilization and outcome of AC in routine practice is described in a few studies, with non-conclusive results.

Materials and methods: This retrospective study included consecutive patients with NSCLC who underwent curative-intent surgery. Data of AC uptake in stages IB (tumor of ≥4 cm in diameter), II, and IIIA, and reasons of AC omission were evaluated according to medical records. Mortality risk among patients treated with surgery (only) and different types of AC in routine practice was compared.

Results: AC was applied to 79% of patients with stages IB (tumor of ≥4 cm in diameter), II, and IIIA, and was associated with an improved median of overall survival (HR = 0.69; 95% CI = 0.44–1.06). Significantly longer survival was achieved in the sub-group treated with platinum and oral vinorelbine (HR = 0.575, 95% CI = 0.339–0.974), and the longest survival was among patients treated with oral vinorelbine and cisplatin (HR = 0.371, 95% CI = 0.168–0.820).

Conclusions: AC utilization should be based on co-operation between surgeons, pneumo-oncologists, and patients. Rational use of AC offers better survival in routine practice.

ARTICLE HISTORY
Received 29 March 2018
Revised 29 May 2018
Accepted 14 June 2018

KEYWORDS
Non-small cell lung cancer; adjuvant chemotherapy uptake; survival; real-world study

Introduction

Lung carcinoma remains the malignity with the greatest case fatality, and its incidence is rising globally. Radical surgery of non-small cell lung cancer (NSCLC) is an optimal solution with favorable survival outcomes[1]. In patients with stages IIA, IIB, and IIIA after complete resection, adjuvant chemotherapy (AC) has become a standard of care. Results obtained for the stage IB were not conclusive, but in tumors of ≥4 cm in diameter AC may also offer survival advantage[2–4]. The primary goal of adjuvant therapy in NSCLC is to eradicate micrometastases, reducing the rate of distant metastases and, thereby, increasing survival following resection[5]. Selection of patients suitable for AC is influenced by the limited gain of AC, which is ~4% in absolute 5-years survival[4]. Significant toxicity and the lack of predictive biomarkers are the other limiting factors[6]. Robust data were processed in phase III trials and large meta-analyses, but there are only a few retrospective population-based studies describing utilization of AC in routine practice where patients have a significant co-morbid disease burden and frequent contraindications to cisplatin-based chemotherapy[7–9]. In regional retrospective studies, use of AC varied substantially in the evaluated sample and methodology, applied chemotherapy was heterogeneous with differing tolerance, and survival was not calculated[10–12]. The present study evaluates the uptake patterns and survival results of AC applied on a routine basis in a specified region with 600,000 inhabitants.

Study subjects and study design

The objective of the study was to describe the uptake of adjuvant chemotherapy, and to evaluate factors which can influence acceptance and compliance to this post-operative therapeutic approach within a non-interventional real-world set up. Another primary objective was to assess survival according to the different treatment modalities chosen; evaluated variables were median of recurrence-free survival (mRFS), 5-year recurrence free survival, median of overall survival (mOS), and 5-year overall survival. Secondary aims were to consider toxicity and compliance with chemotherapy. This retrospective study involved patients with NSCLC who underwent curative-intent surgery between January 12, 2006 and December 11, 2013. Consecutive patients with NSCLC stages IB (tumor of ≥4 cm in diameter), IIA, IIB, and IIIA were considered suitable for AC. Patients were diagnosed in a tertiary pneumological department, underwent tumor resection, and

CONTACT Vítězslav Kolek vitezslav.kolek@fnol.cz Department of Respiratory Medicine, University Hospital Olomouc, I.P. Pavlova 185/6, Nová Ulice, 779 00 Olomouc, Czech Republic

were subsequently referred to pneumo-oncologists in the same hospital. The benefit and risk of AC, as well as chemotherapy options were properly discussed with patients and with colleagues at regular interdisciplinary tumor board meetings. Data of AC were collected from medical records. Demographic and clinical parameters were evaluated in subgroups with AC and surgery only (SO). Reasons for AC omission were discussed. Survival data were compared between patients with AC and SO, between different types of AC used, and according to various cofactors, including patient sex, PS, age at diagnosis, smoking history, presence of comorbidities (cardiac, respiratory, hepatic, metabolic, renal, or neurological), type of surgery, pathological stage of disease, lung cancer grading, histopathology, pleural invasion, and angio-invasion.

Ethical and legal frame

The study was initiated by the Department of Respiratory Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic, and was conducted as a fully observed study under real world conditions. The retrospective evaluation was conducted upon approval of an Ethics Committee, obtained as part of an academic grant IGA MZ ČR NT 13569 supported by the Czech Ministry of Health, and the results were evaluated under the framework of the grant AZV 16-32318 A, supported by the Czech Health Research Council. The study was performed in compliance with the applicable legislation and the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Methods

Medication

Patients received the first cycle of treatment within 2–6 weeks of surgery. Four cycles of 21 days AC were planned. Pre-medication was undertaken using dexamethasone or setrons when needed. Most frequently, platinum doublets with oral vinorelbine were applied: cisplatin (CDDP) 80 mg/m^2 + vinorelbine (D1 i.v. 25 mg/m^2, D8 p.o. 60 mg/m^2), carboplatin (CBDCA) – AUC 5 + vinorelbine (D1 i.v. 25 mg/m^2, D8 p.o. 60 mg/m^2), CDDP 80 mg/m^2 + vinorelbine (D1 and D8 60 mg/m^2 p.o. with escalation to 80 mg/m^2 p.o.), CBDCA – AUC 5 + vinorelbine (D1 and D8 60 mg/m^2 p.o. with escalation to 80 mg/m^2 p.o.). Other doublets on an intravenous basis were: CBDCA- AUC6 + paclitaxel (D1 100 mg/m^2), CDDP 80 mg/m^2 + gemcitabine (D1,8 1200 mg/m^2), CDDP 80 mg/m^2 + docetaxel (D1 75 mg/m^2), and CBDCA- AUC6 + vinorelbine (D1 and D8 25 mg/m^2 i.v.). In some patients with NSCLC stage IIIA, adjuvant chemotherapy was applied after three cycles of neoadjuvant chemotherapy (NC): CBDCA – AUC6 + paclitaxel (D1 100 mg/m^2), CDDP 80 mg/m^2 + gemcitabine (D1,8 1200 mg/m^2) and CDDP 80 mg/m^2 + docetaxel (D1 75 mg/m^2). Dosage of CBDCA was calculated by Calvert's formula using a calculated creatinine clearance with the Cockcroft–Gault formula[13]. Treatment with oral vinorelbine and most of the other regimens were applied on an out-treatment basis. Patients eligible for AC were selected if fulfilling the following criteria: patients with stages IB, IIA, IIB, and IIIA NSCLC as of 7th TNM classification after complete resection, ECOG 0–2, age $\geq$18, and $\leq$75 years[14]. Limits of laboratory values: le $>$3.5 G/l, neu $>$1.5 G/l, tr $>$100 G/l, AST $<1.5 \times$ N, ALT $<1.5 \times$ N. AC was offered to patients without prolonged surgical complications, worsening of co-morbid conditions or pre-existing internal disease. Oral vinorelbine was offered, especially to patients showing the potential for good compliance to out-patient treatment[15,16]. Generally, radiotherapy was offered in N2 stages.

Follow-up

The stage of disease was reassessed at the end of the 4th cycle of chemotherapy using chest X-ray and CT of chest and upper abdomen. Bronchoscopy was performed only when endobronchial progression was suspected. Bone scintigraphy was conducted where hypercalcinemia or increased alkaline phosphatases were observed, or bone pain was reported by the patient. Brain CT was performed if neurological impairments were present. A detailed restaging was then further performed at half-year intervals and where recurrent disease was suspected.

Statistical analysis

This was an explorative study. Logistic regression models and discriminant function analyses were employed to identify co-factors associated with the utilization and efficacy of AC. Patient characteristics were summarized using frequency tables and standard descriptive statistics such as mean (95% confidence intervals), SD, variance, min, max, median, Q2, and Q3. The statistical significance of observed difference in proportions was tested using the χ^2 test and Fisher's exact test when data were sparse. The Wilcoxon Two Sample test was used to determine the significance between differences in medians. The Kaplan-Meier method was used to calculate estimates of overall survival and recurrence-free survival. Differences in these estimates were tested for significance using the Log-rank statistic. The Hazard Ratio +95% CI was calculated by the Cox Regression Hazard Model. Overall survival was defined as the time from study entry to death from any cause. Recurrence-free survival was defined as the time from study entry to failure at the end of two courses, relapse, or death from any cause. Survival characteristics were further tested using a log-rank test to compare the survival distributions in the presence of the following factors and co-variates: age, gender, histology, stage, smoking, and type of surgery. Statistical significance was determined for all statistical tests at the level of 5%. Statistical analysis was performed using the software SW SAS (Cary, NC) and SW Statistica (StatSoft, Inc., Tulsa, OK).

Results

Out of all 1557 patients with lung cancer diagnosed during the evaluation period, NSCLC was present in 1293 patients. Three hundred and eight patients underwent curative-intent surgery and complete resection was achieved in 284 patients. AC was not indicated in 95 patients due to stage IA or IB with tumor size of <4 cm. AC was considered in 189 patients with stages IB (tumor of ≥4 cm in diameter), IIA, IIB, and IIIA. The mean age of the evaluated series was 64.3 years, 134 (70.8%) were men, 55 (29.2%) women; 94 (49.7%) were current smokers, 75 (39.7%) ex-smokers, and 20 (10.6%) non-smokers. Median of follow up was 3.1 years (6.2 years in censored patients). AC was applied in 149 patients (78.8%), including 34 (18.0%) patients with neoadjuvant chemotherapy (NC), AC was not applied in 40 (21.2%) patients. The absence of AC was predominantly due to worsening health status as a consequence of co-morbidities or surgical complications, sometimes present simultaneously; only six patients declined due to personal reasons (Table 1). Sub-groups of AC and SO differed significantly in mean age (63.3 vs 68.6 years), co-morbidities (63% vs 75% having ≥2 co-morbidities), TNM stages (63% vs 80% having stage I/II) and PS (45.2% vs 20.0% having PS 0). There was a trend to a smaller number of pneumonectomies (6% vs 25%). There were no significant differences in sex, smoking history, or histology of lung cancer (Table 2). Similar trends favored carboplatin or cisplatin when given in different doublets.

Compared to 26 patients with cisplatin, 89 patients with carboplatin were significantly older (65.0 vs 57.2 years, $p < .0001$), with higher PS (37.1% vs 73.1% having PS 0, $p = .0012$) and with a higher number of co-morbidities (70.8% vs 38.5% having ≥2 co-morbidities, $p = .0026$). In the sub-groups receiving oral vinorelbine and platinum doublets, similar differences were noted between those receiving carboplatin (69 patients) or cisplatin (21 patients): age 64.9 vs 56.8 years, $p = .0008$, PS 0 44.9% vs 85.7%, $p = .0010$ and co-morbidities 6.2% vs 38.1%, $p = .0270$.

Table 1. Reasons for adjuvant chemotherapy omission.

Reason	*n*	%
Patient declined	6	15.00
Surgical complications	18	45.00
Pneumonia	9	22.50
Pneumothorax	2	5.00
Fistula	2	5.00
Other surgical complications	5	12.50
Internal complications	21	52.50
Heart failure	11	27.50
Metabolic disbalance	4	10.00
Renal failure	2	5.00
Other co-morbidity	4	10.00

Table 2. Differences between sub-groups of patients with adjuvant chemotherapy after surgery or patients with surgery only.

	AC (*n*)	AC (%)	SO (*n*)	SO (%)	*p*
Total number	115	100	40	100	–
Men	80	69.57	28	70.00	.9589*
Women	35	30.43	12	30.00	
Mean age (years)	63.25		68.55		.0046**
Comorbidities (0, 1)	42	36.52	10	25.00	.1837*
Comorbidities (≥2)	73	63.48	30	75.00	
Adenocarcinoma	41	35.65	18	45.00	.5769*
Squamous carcinoma	64	55.65	19	47.50	
NOS	10	8.70	3	7.50	
Stage IB, II	73	63.48	32	80.00	.0023***
Stage III	42	36.52	8	20.00	
Pneumonectomy	7	6.09	10	25.00	.0542*
Other type of surgery	108	93.91	30	75.00	
Ex-smoker and non-smoker	57	49.57	21	52.50	.7491*
Smoker	58	50.43	19	47.50	
Grade 1 and 2	41	35.65	14	35.00	.9408*
Grade 3 and 4	74	64.35	26	65.00	
PS 0	52	45.22	8	20.00	.0048*
PS 1 and 2	63	54.78	32	80.00	

Abbreviations. AC, adjuvant chemotherapy; SO, surgery only; NOS, no other specified tumor; PS, performance status.

Survival

The total series (189 patients) had mRFS 2.29 (95% CI = 1.470–3.570) years, 5-years RFS 37.7%, mOS 3.26 (95% CI = 2.480–5.170) years, and 5-year OS 43.14%. Survival variables of sub-groups are listed in Table 3 (RFS) and Table 4 (OS). Survival parameters of patients with AC were longer than the survival data of patients with SO, but the difference was not statistically significant (the HR in mRFS was 0.740, in mOS the HR was 0.679) (Figure 1). Patients treated with oral vinorelbine and platinum doublets lived significantly longer than patients with SO (mOS = 4.47 years and 5-year OS = 49.15%) (Figure 2). Patients treated with oral vinorelbine and platinum doublets survived significantly longer than patients treated with all other chemotherapies (for RFS, $p = .0455$, HR = 0.601; for mOS, $p = .0368$ and HR = 0.575) (Figure 3). The longest survival was observed in patients treated with oral vinorelbine with cisplatin (mOS not reached, 5-year OS 65.19%) (Figure 4). Patients receiving neoadjuvant–surgery–adjuvant combination were not statistically compared because of different selection strategies (mOS = 3.850 years, 95% CI = 1.680–7.110, 5-year OS = 45.64%).

Survival according to co-factors

Different specific co-factors influencing survival were evaluated in both univariate and multivariate analyses. In the univariate analysis, survival was significantly longer in patients with PS 0 than PS 1/2 ($p = .0008$, HR = 0.455, 95% CI = 0.283–0.731), in TNM stages I/II than in TNM stage IIIA ($p = .0010$, HR = 0.444, 95% CI = 0.269–0.731) and significantly shorter in tumors with angioinvasion ($p = .0222$, HR = 0.508, 95% CI = 0.281–0.919). In a Cox regression multivariate analysis, significant changes in mOS were present only between TNM stages ($p = .0071$, HR = 0.479, 95% CI = 0.280–0.818) and PS ($p = .0075$, HR = 0.452, 95% CI = 0.253–0.809). Age, sex, smoking habits of patients, type of surgery, grade, histology, and pleural invasion of tumor had no significant impact on survival. There was a trend towards worse survival of patients after pneumonectomy ($p = .0527$) in the univariate analysis, and a trend towards

Table 3. Parameters of recurrence-free survival in patients with different types of adjuvant chemotherapy or with surgery only.

Sub-group	*n*	mRFS	mRFS (95% CI)	5-year RFS	*p*-value (Log-rank test)	HR	HR 95% CI
SO	40	1.480	0.490–3.460	28.00%	reference	reference	reference
AC	115	2.390	1.450–3.800	39.00%	.1709	0.740	0.479–1.141
AC vin o	90	2.455	1.450–6.630	42.74%	.0845	0.671	0.426–1.059
AC vin o + cis	21	NA	NA	52.50%	.0417	0.480	0.233–0.989
AC other	25	2.290	0.930–3.990	26.00%	.8877	1.042	0.591–1.836

Abbreviations. SO, surgery only; AC, adjuvant chemotherapy; AC vin o, oral vinorelbine plus platinum; AC vin o + cis, oral vinorelbine with cisplatin; AC other, other chemotherapy than vinorelbine oral in combination with platinum; mRFS, median recurrence free survival.

Table 4. Parameters of overall survival in patients without adjuvant chemotherapy or with different types of adjuvant chemotherapy.

Sub-group	*n*	mOS	mOS (95% CI)	5-year OS	*p* (Log-rank test)	HR	HR (95% CI)
SO	40	1.955	0.530–5.350	37.50%	reference	reference	reference
AC	115	3.730	2.480–5.870	44.59%	.0855	0.679	0.435–1.059
AC vin o	90	4.470	2.700–7.860	49.15%	.0372	0.575	0.339–0.974
AC vin o + cis	21	NA	0.3730–NA	65.19%	.0107	0.371	0.168–0.820
AC other	25	2.760	1.120–4.490	28.20%	.9806	0.993	0.551–1.788

Abbreviations. SO, surgery only; AC, adjuvant chemotherapy; AC vin o, oral vinorelbine plus platinum; AC vin o + cis, oral vinorelbine with cisplatin; AC other, other chemotherapy than vinorelbine oral in combination with platinum; mOS, median overall survival.

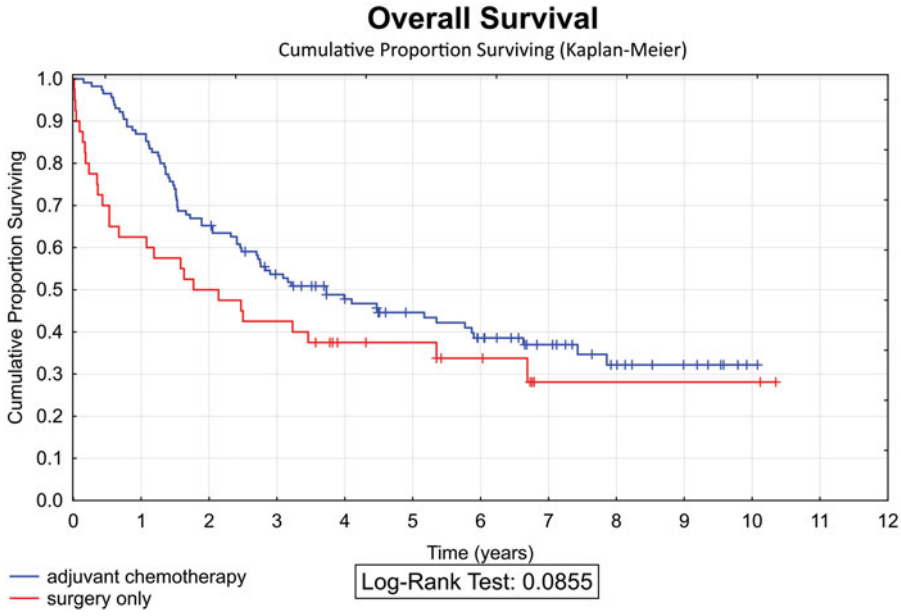

Figure 1. Kaplan-Meier curve of survival in patients with adjuvant chemotherapy or without chemotherapy (surgery only).

worse survival in tumors with angioinvasion ($p = .0616$) in the multivariate analysis.

Toxicity and compliance

The toxicity of AC was acceptable. The most frequent side-effect of Grade 3/4 was neutropenia, which appeared in 34.4% of patients, followed by nausea in 33.3%, leucopenia in 8.8%, anemia in 5.6%, diarrhea in 5.6%, and thrombocytopenia in 3.3%. Febrile neutropenia appeared in 2.2% of patients. Compliance with oral vinorelbine based AC was especially high, with 82% of patients completing their planned therapy. The average number of cycles per patient was 3.87. In other types of AC, 69% of patients accomplished all four planned cycles.

Discussion

The diagnosis of early NSCLC remains an unfulfilled need and screening based on low dose computed tomography, potentially combined with blood or exhaled breath condensate analysis, provides an opportunity to increase the early detection of those lung tumors which can be resolved by surgical resection[17,18]. A number of large clinical studies have revealed that AC improves overall survival for patients with higher risk resected NSCLC[19–22]. The LACE study reported a hazard ratio of 0.89 for OS, a 5-years improvement of OS by 5.4% for those on cisplatin-based AC[3]. Larger meta-analysis revealed a 5-year survival gain of only 4%. One of the issues in this study was that only 50–58% of patients completed the planned therapy[3,4]. In accordance with these trials, current guidelines recommend adjuvant cisplatin-based

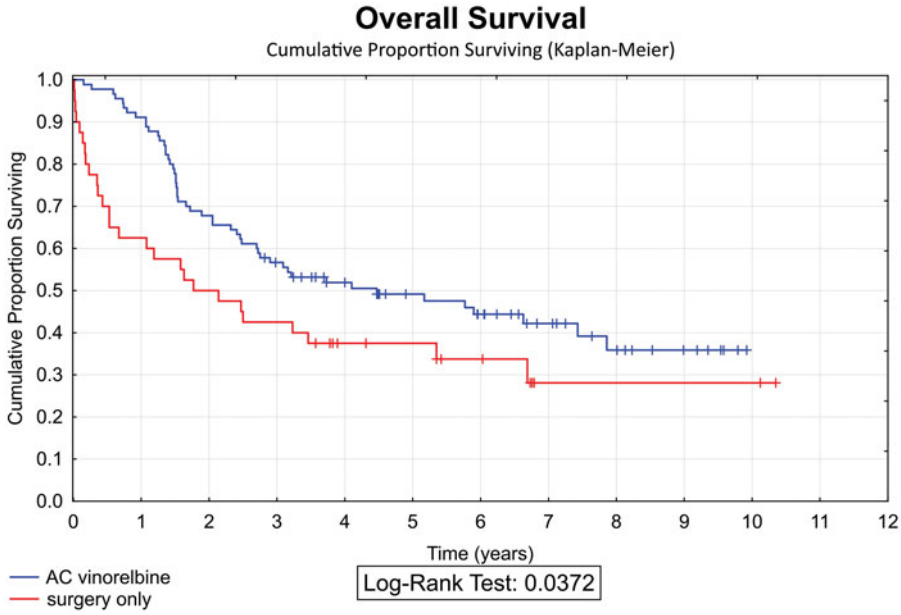

Figure 2. Survival in patients treated with a combination of oral vinorelbine plus platinum and in patients with surgery only.

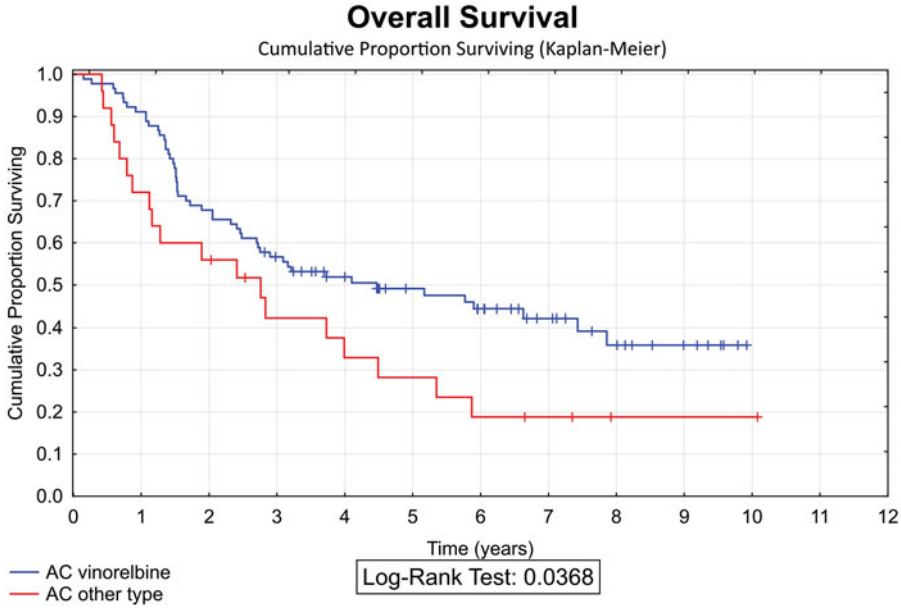

Figure 3. Survival in patients treated with a combination of oral vinorelbine plus cisplatin and surgery only.

doublet AC, preferably with vinorelbine. The overall survival impact of AC, however, depends upon its uptake outside of these clinical trials, among patients with significant co-morbid disease burden and frequent contraindications to cisplatin-based chemotherapy. Canadian and American population-based studies show that evidence from randomized trials and meta-analyses performed within the last decade have had a great impact on clinical practice for non-metastatic NSCLC[7,9]. The uptake of AC rose from 7% to 31% in large population data analyses (2001 to 2006), and it was even higher in stages II and IIIA. In these studies, AC uptake was influenced by the type of insurance, socio-economic status, marital status, level of education, and number of co-morbidities[7–9]. In a Canadian study with 108 surgical patients, only 44% were referred back to an oncologist after resection, and 39% of them refused the recommended AC[10]. Following major surgery, AC was administered to 22 patients, predominantly with Stages II and IIIA, who were aged under 65 and lived close to the medical center[10].

A similar Canadian study with 204 patients increased the percentage of referred patients from 31% to 63% after the presentation of large scale adjuvant trials (2003 to 2005)[11]. In 50% of cases, the reason for not prescribing adjuvant chemotherapy was patient refusal[11].

In a French study with 219 patients, uptake of AC was 40%, but only 38% of patients with AC completed the planned therapy, which was considerably heterogeneous[12].

Our study proved that the uptake of AC after NSCLC resection can be high (79%). One of the most important factors seems to be regular co-operation between surgeons,

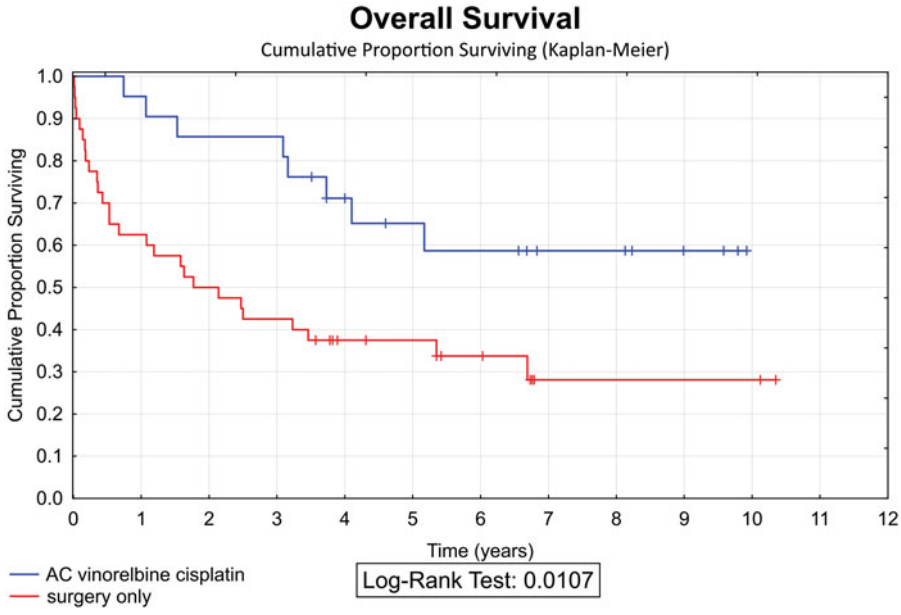

Figure 4. Survival in patients treated with oral vinorelbine with platinum and with all other chemotherapies.

pneumo-oncologists, and patients in the framework of a single institution. The direct consequence was almost 100% of patients referred to an oncologist in the present study. Another factor can be the choice of AC. Due to possible side-effects and even treatment-related deaths of cisplatin adjuvant regimens, carboplatin is frequently preferred in routine practice[6,8,23,24]. Higher tolerability can influence the AC uptake in older patients, and in a large study on patients older than 65 years in the SEER-Medicare there was no survival difference observed between cisplatin and carboplatin-based AC after lung cancer resection[25]. Compliance with AC was higher when carboplatin was used[6,26]. Patient perception of the efficacy of oral as opposed to parenteral therapy can also be an issue[27–29].

In the present study, patients who received AC had longer mOS than patients with SO with an absolute 5-years survival benefit of 11% (HR = 0.69; 95% CI = 0.44–1.06). Significantly longer survival was achieved in the sub-group treated with platinum and oral vinorelbine (HR = 0.575, 95% CI = 0.339–0.974), and the longest survival was among patients treated with oral vinorelbine and cisplatin (HR = 0.371, 95% CI = 0.168–0.820). This accords with AC effectiveness, but, in routine practice non-randomized studies, the rational use of AC and the choice of different chemotherapeutic regimens according to age and polymorbidity of patients also plays a substantial role. In the present series, AC was applied in younger patients with lower PS, less co-morbidities, and higher TNM stages. A more aggressive regimen with cisplatin was applied in younger patients with reduced polymorbidity and lower PS than a sub-group of patients treated with carboplatin. Survival of patients with AC in the present series was influenced by many co-factors, such as TNM staging, performance status, and vascular invasion in the tumor. These results are similar to previously published multi-center randomized Phase III trials[30–32].

Personalization of AC is currently difficult without reliably predictive biomarkers, and can be based only on the choice of effective chemotherapy, with regard to potential adverse events. Attempts to improve outcomes of AC with the addition of other agents to platinum doublets have been disappointing, including the negative trial with bevacizumab and MAGE-A3 vaccine[33,34]. Trials with EGFR TKIs brought some promising but immature data in selected EGFR positive subsets, which cannot be considered as a preferred approach until the OS results show clear benefits to support this approach instead of proven benefits of standard AC[35,36]. It is also too early to comment on running trials with modern immuno-oncotherapy like checkpoint inhibitors.

Conclusions

The chemotherapy utilization rates in patients with resected NSCLC in everyday practice can be high. The dominant factor is an effective multidisciplinary tumor board and an intensive cooperation between surgeons and pneumo-oncologists in the framework of a single institution. AC should be discussed with patients on an individual basis. The acceptance of AC was related to age, PS, and TNM stage. AC was not applied in patients with more co-morbidities and more demanding surgery, but only rarely due to patient refusal. The present study demonstrated a longer survival of patients selected for AC than the survival of patients with surgery only. The longest survival was documented in patients treated with the doublet of cisplatin and oral vinorelbine, which was applied to younger patients with lower PS and less co-morbidities. Survival results were influenced by PS, TNM stage, and angio-invasion of the tumor. The preferably chosen AC with oral vinorelbine had good compliance, a high percentage of completed therapeutic schedules, and satisfactory survival.

Transparency

Declaration of funding

This work was supported by the Czech health research council under grant AZV 16-32318A.

Declaration of financial/other interests

The authors have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The authors acknowledge the assistance of Michael K. Hill in the preparation of this manuscript and the statistics calculation of Stanislav Kormunda.

References

1. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36
2. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899-909
3. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. J Clin Oncol 2008;26:3552-9
4. NSCLC Meta-analysis Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;357:1267-77
5. Coello MC, Luketich JD, Litle VR, et al. Prognostic significance of micrometastasis in non-small-cell lung cancer. Clin Lung Cancer 2004;5:214-25
6. Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study. BMJ 2011;343:247-51
7. Booth CM, Shepherd FA, Peng Y, et al. Adoption of adjuvant chemotherapy for non-small-cell lung cancer: a population-based outcomes study. J Clin Oncol 2010;28:3472-8
8. Williams CD, Garja A, Ganti AK, et al. Use and impact of adjuvant chemotherapy in patients with resected non-small cell lung cancer. Cancer 2014;120:1939-47
9. Goyal G, Silberstein PT. Impact of demographic and health system factors on adjuvant chemotherapy use in stage II non-small cell lung carcinoma: a national cancer database analysis from 2000 to 2012, p 3056. Presented at WCLC 2015, Denver, CO, September 6–9, 2015
10. Younis T, Al-Fayea T, Virik K, et al. Adjuvant chemotherapy uptake in non-small cell lung cancer. J Thorac Oncol 2008;3:1272-8
11. Kassam F, Shepherd FA, Johnston M, et al. Referral patterns for adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. J Thorac Oncol 2007;2:39-43
12. Massard C, Tran Ba Loc P, Haddad V, et al. Use of adjuvant chemotherapy in non-small cell lung cancer in routine practice. J Thorac Oncol 2009;4:1504-10
13. Hryniuk WM, Goodyear M. The calculation of received dose intensity. J Clin Oncol 1990;8:1935-7
14. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14
15. Jassem J, Ramlau R, Karnicka-Młodkowska H, et al. A multicenter Randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients. Ann Oncol 2001;12:1375-81
16. Jensen LH, Osterlind K, Rytter C. Randomized cross-over study of patient preference for oral or intravenous vinorelbine in combination with carboplatin in the treatment of advanced NSCLC. Lung Cancer 2008;62:85-91
17. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409
18. Youssef O, Knuuttila A, Piirila P, et al. Presence of cancer associated mutations in exhaled breath condensates of healthy individuals by next generation sequencing. Oncotarget 2017;8:18166-76
19. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small cell lung cancer. J Natl Cancer Inst 2003;95:1453-61
20. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-60
21. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27
22. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. Engl J Med 2005;352:2589-97
23. Speicher PJ, Gu L, Wang X, et al. Adjuvant chemotherapy after lobectomy for T1–2N0 non-small cell lung cancer: are the guidelines supported? J Natl Compr Canc Netw 2015;13:755-61
24. Stinchcombe TE, Harper HD, Hensing TA, et al. The feasibility of adjuvant carboplatin and docetaxel in patients with curatively resected non-small cell lung cancer. J Thorac Oncol 2008;3:145-51
25. Gu F, Strauss GM, Wisnivesky JP. Platinum-based adjuvant chemotherapy (ACT) in elderly patients with non-small cell lung cancer (NSCLC) in the SEER-Medicare database: comparison between carboplatin- and cisplatin-based regimens. J Clin Oncol 2011;29(15 suppl):7014
26. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51
27. Sorensen SF, Carus A, Meldgaard P. Intravenous or oral administration of vinorelbine in adjuvant chemotherapy with cisplatin and vinorelbine for resected NSCLC. Lung Cancer 2015;88:167-73
28. O'Brien MER, Szczesna A, Karnicka H, et al. Vinorelbine alternating oral and intravenous plus carboplatin in advanced non-small-cell lung cancer: results of a multicentre phase II study. Ann Oncol 2004;15:921-4
29. Catania C, Didier F, Leon ME, et al. Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer. Breast Cancer Res Treat 2005;92:265-72
30. Sedrakyan A, Van Der Meulen J, O'Byrne K, et al. Postoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2004;128:414-19
31. Bria E, Gralla RJ, Raftopoulos H, et al. Magnitude of benefit of adjuvant chemotherapy for non-small cell lung cancer: meta-analysis of randomized clinical trials. Lung Cancer 2009;63:50-7
32. Cortés ÁA, Urquizu LC, Cubero JH. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res 2015;4:191-7

33. Wakelee HA, Dahlberg SE, Keller SM. Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected non-small cell lung cancer (NSCLC): results of E1505. J Thorac Oncol Proc WCLC, 2015; Abstr:Plen04.03, 2015
34. Vansteenkiste JF, Cho BC, Vanakesa T, et al. Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3 positive non-small cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:822-35
35. Kelly K, Altorski NK, Eberhrdt WE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non small-cell lung cancer (RADIANT): a randomized double blind, phase III trial. J Clin Oncol 2015;33:4007-14
36. Zhong WZ, Wan Q,Mao WM, et al: Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncology 2018;19(1):139-148