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A randomized trial comparing adjuvant chemotherapy with gemcitabine plus cisplatin with docetaxel plus cisplatin in patients with completely resected non-small-cell lung cancer with quality of life as the primary objective

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Abstract

OBJECTIVES: Adjuvant chemotherapy with vinorelbine plus cisplatin (VC) improves survival in resected non-small-cell lung cancer (NSCLC), but has negative impact on quality of life (QoL). In advanced NSCLC, gemcitabine plus cisplatin (GC) and docetaxel plus cisplatin (DC) exhibit comparable efficacy, with possibly superior QoL compared to VC. This trial investigated these regimens in the adjuvant setting.

METHODS: Patients with Stage IB to III NSCLC were eligible following standardized surgery. Overall, 136 patients were included, with 67 and 69 assigned to the GC and DC arms, respectively. Cisplatin (75 mg/m², Day [D] 1) plus gemcitabine (1250 mg/m², D1 and D8) or docetaxel (75 mg/m² D1) were administered for three cycles. Primary end-point was QoL (EORTC QLQ-C30), with the study designed to detect a 10-point difference between arms. Overall survival, safety and cost were secondary end-points.

RESULTS: No between-group imbalance was observed in terms of patient characteristics. At inclusion, global health status (GHS) scores (/100) were 63.5 and 62.7 in GC and DC, respectively ($P = 0.8$), improving to 64.5 and 65.4 after 3 months ($P = 0.8$). No significant difference in functional or symptoms scores was observed between the arms except for alopecia. Grade 3/4 haematological and non-haematological toxicities were found in 33.8 and 21.7% ($P = 0.11$), and 33.8 and 26.1% ($P = 0.33$) of patients, in GC and DC, respectively. At 2 years, 92.9 and 89.8% of patients remained alive in GC and DC, respectively ($P = 0.88$).

CONCLUSIONS: DC and GC adjuvant chemotherapies for completely resected NSCLC were well tolerated and appear free of major QoL effects, and are therefore representing candidates for comparison with the standard VC regimen.

Keywords: Non-small-cell lung cancer • Adjuvant chemotherapy • Quality of life

INTRODUCTION

Only 15–20% of lung cancer cases are diagnosed at an early stage and thus make the patient eligible for thoracic surgery, such as lobectomy or pneumonectomy plus radical lymph node dissection. However, 5-year survival rates for patients with pathological staged IA–IIB non-small-cell lung cancer (NSCLC) average 50%, and adjuvant chemotherapy is the standard of care for patients with Stage II–III resected NSCLC [1, 2], with an absolute benefit of 5.4% at 5 years, especially when using vinorelbine plus cisplatin (VC) [3–5].

While the benefit of adjuvant chemotherapy has been demonstrated, the optimal regimen remains to be established. Long-term side-effects have been singled out in the older regimens [6], and the VC combination is associated with a negative impact on quality of life (QoL), although it does improve survival in patients with resected NSCLC [7]. In advanced-stage NSCLC, gemcitabine plus cisplatin (GC) and docetaxel plus cisplatin (DC) combinations have comparable efficacy and may be superior to VC in terms of QoL outcomes.

This trial was therefore designed to provide data, and especially data on QoL outcomes, on GC and DC adjuvant regimens for patients with resected NSCLC, in order to select a potential new comparator to the VC regimen.

MATERIALS AND METHODS

Global study design

This study was designed in 2003 as a randomized trial of adjuvant GC versus DC regimens after complete resection of Stage IB–III NSCLC with the objective to eventually select the regimen with the lower impact on postoperative QoL. It began in September 2004.

The protocol was conducted in accordance with the Helsinki Declaration and Good Clinical Practice guidelines, and was approved by the *Comité de Protection des Personnes Marseille 2* (French ethics review board) in September 2004. All patients signed written informed consent before enrolment. Because patient enrolment began before 1 November 2006, the trial was not registered on the clinical trials website. However, the methodology was published at the time of the initiation of the trial [8].

Patient eligibility

Patients aged 18–75 years with completely resected (R0) Stage IB–III NSCLC in addition to an Eastern Cooperative Oncology Group performance status of 0 or 1 were eligible for entry into this study. Surgery was standardized on the following basis. First, anatomical resection with lobectomy or pneumonectomy was defined as the standard resection for fit patients, thus excluding sublobar resections, that is, segmentectomy and wedge resections. Secondly, reinforcement of the main-stem bronchial suture line was carried out as a matter of routine in cases of right pneumonectomy. Thirdly, routine mediastinal lymphadenectomy was considered an essential component of NSCLC thoracic surgery. Operative reports were also required to include the following information: description of the tumour and its connections with surrounding anatomical structures; surgeon's justification for the choice of resection performed; completeness of the resection; lymph node stations

dissected according to the staging criteria of the American Joint Committee on Cancer [9].

Patients were required to have adequate bone marrow reserve and organ function, including calculated creatinine clearance of 45 ml/min based on the standard Cockcroft and Gault formula. Patients with severe postoperative complications (acute respiratory distress syndrome, bronchial fistula or severe pneumonia) were ineligible. Patients with previous history of cancer within the previous 5 years or clinically significant cardiac dysfunction, active infection or neurological/psychiatric disorders were also excluded from participating in the study.

Treatment plan

Within 6 weeks after the standardized thoracic surgery, eligible patients were randomly assigned in a 1:1 ratio to adjuvant GC or DC chemotherapy. Stratification was done according to the pathological tumour-node-metastasis (pTNM) staging as being in Stages IB, II or III and centre.

Treatment started within 2 weeks of randomization. Consequently, chemotherapy was started no more than 8 weeks after surgery and consisted of cisplatin (75 mg/m², D1) plus gemcitabine (1250 mg/m², D2 and D8) or docetaxel (75 mg/m², D1) for three cycles. At the time of the trial design, the number of postoperative chemotherapy cycles was not firmly determined and three cycles were deemed to be sufficient as in the NATCH trial design. Eligible patients received a platinum-based doublet with 75 mg/m² cisplatin on Day (D) 1 plus either 1250 mg/m² gemcitabine on D1 and D8 or 75 mg/m² docetaxel on D1 every 3 weeks for a maximum of three cycles. Chemotherapy was adjusted for toxicity according to protocol guidelines. Patients requiring a reduction in the gemcitabine, docetaxel or cisplatin doses received on D1 were given the reduced dose for the remainder of the study. Therapy was discontinued in patients who, after already having had two dose reductions since their initial D1 dose, experienced toxicity requiring a third dose reduction. Cycle delays of up to 35 days were permitted for recovery from adverse events. Supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were permitted according to the American Society of Clinical Oncology (ASCO) guidelines. Postoperative radiotherapy for patients with pN2 disease was not mandatory, this decision being left to the participating centre. Postoperative radiotherapy had to be decided on prior to patients' inclusion in the trial. Radiotherapy was allowed at doses ranging from 45 to 60 Gy, 2 Gy per fraction, with five fractions per week, starting 4 weeks after the end of chemotherapy.

Baseline and follow-up assessments

QoL was assessed using the EORTC QLQ-C30 and the lung cancer questionnaire module QLQ-LC13, two validated QoL tools available in French [10–14]. The QLQ-C30 comprises 30 questions covering five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain and nausea/vomiting) and a global health status (GHS)/QoL scale, as well as six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Raw scores from each functional and symptom scale were translated onto an overall scale ranging from 0 to 100. Higher functional scores were indicative of better QoL, whereas lower symptom and single item scores reflected fewer symptoms. Patients were asked to complete a baseline QoL

assessment within the 14 days of screening and then at Weeks 1 (start of chemotherapy), 3 (D1 cycle 2), 6 (D1 cycle 3) and 9 (end of chemotherapy) during chemotherapy, at months 3, 6 and 12 after randomization, at scheduled clinic appointments.

Before entering the study, patients underwent a physical examination and radiological assessment by CT (computed tomography) scan of the chest, upper abdomen and brain. Physical examinations and chest X-rays were performed at D1 of each chemotherapy cycle. The follow-up clinical examinations and radiological assessment (alternately chest X-ray and CT scan of the chest, upper abdomen and brain) were performed 4 weeks after the end of treatment and then every 3 months for 2 years, and every 6 months thereafter for up to 5 years. All patients who received at least one dose of cisplatin plus either gemcitabine or docetaxel were considered assessable for safety. Patients were assessed for toxicity according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v2.pdf). Efficacy analyses incorporated all enrolled patients on an intent-to-treat basis.

Statistical analyses

The primary end-point was QoL, assessed 3 weeks after the end of chemotherapy (evaluation at the end of chemotherapy at Week 9) using the Quality of Life Questionnaire EORTC QLQ-C30. The trial was designed to detect a 10-point difference in QoL scores on the global scale ($\alpha = 0.05$, power 80%) between the arms. Secondary end-points included overall survival (OS), disease-free survival (DFS), toxicity and costs. Cost data will be presented separately.

Compliance with QoL data collection was expressed as the percentage of eligible patients expected to complete the QoL questionnaire at a certain time point. Patients were censored in the event of disease relapse or death from any cause.

A change in score of 10 points from baseline was defined as clinically significant on the basis of previous studies [7] and published guidelines [15, 16]. A sample size of 63 patients per arm (i.e. 126 patients in total) was required to provide the trial with 80% power in order to detect a 10-point difference in QoL score between the two adjuvant chemotherapy arms, with a two-sided 5% significance level. The sample size was increased by 10% to 150 patients taking in order to minimize the impact of patients lost to the follow-up. Accrual in the trial was prematurely stopped by the steering committee in December 2007 following the release of new ASCO recommendations, which proposed four cycles of adjuvant therapy as the standard, and excluding patients with Stage pIB from adjuvant chemotherapy.

The χ^2 test was performed in order to compare data between the two study arms. The Wilcoxon rank-sum test was used to compare changes between treatment arms in QoL score at each assessment time from baseline. The Kaplan-Meier product-limit method was used to summarize DFS and OS distributions. All tests on treatment effects were two-sided, unless otherwise stated.

RESULTS

Patients

Between August 2004 and December 2007, 136 patients with resected NSCLC and without major postoperative complications

were enrolled in the study from 10 institutions. Figure 1 illustrates the flow diagram of the study. The median age was 57 years, with 74% of the patients being male (Table 1). The study was prematurely closed by the steering committee, but more than the required 126 patients had been included, allowing for full analysis of the trial.

As regards the TNM classification, 32% of patients were staged IB, 34% were staged II and 34% were staged III. In terms of histology, 55% of patients exhibited adenocarcinomas, whereas 23% exhibited squamous cell carcinomas. The remaining patients showed other histological types. In 85% of cases, surgery consisted of (bi)lobectomy. Out of the total number of patients, 67 were assigned to the GC arm and 69 to the DC arm. No significant difference was observed in terms of patient characteristics between the two arms, as given in Table 1.

Quality of life

Compliance with QoL assessment was 100% at baseline, 98% at C1D1 (Week 1), 95% at C2D1 (Week 3), 86% at C3D1 (Week 6) and 71% at the end of chemotherapy (Week 9), meaning that for these patients, the QoL questionnaires were properly filled out, complete and suitable for evaluation.

At inclusion, GHS scores (/100) were 63.5 in the GC arm and 62.7 in the DC arm ($P = 0.8$), improving to 64.5 and 65.4, respectively, after the 3-month treatment period ($P = 0.8$) (Fig. 2). Similarly, for the other functional scores, there were no significant differences between the two treatment groups. The social function was not altered by the number of infusions (Days 1 and 8 for the GC arm) as attested by Fig. 2. In terms of symptom scores, there were no significant between-group differences except for alopecia, where the DC arm showed a significantly higher score than the GC arm (Figs 3 and 4).

Compliance with QoL assessment after 12 months was too low to allow any conclusion (data not shown).

Safety

Chemotherapy compliance was satisfactory, with 80.6 and 85.5% of the patients in the GC and DC arms, respectively, completing all the three planned cycles of chemotherapy.

Overall, 32.8 and 21.7% of patients in the GC arm and the DC arm, respectively, experienced Grade 3/4 haematological toxicities, with no significant difference observed between the arms (Table 2). A significant difference was observed for alopecia only with 13.0% of patients affected in the DC arm versus 3.0% in the GC arm (Table 2).

Overall survival

The median follow-up for the two arms was 20.2 months. At 1 year, 100 and 96.8% of patients remained alive in the GC and DC arms, respectively, this figure being reduced to 92.9 and 89.8% after 2 years ($P = 0.88$), yielding no significant difference between the two arms (log-rank) (Fig. 5). In the course of the study, 15 deaths occurred, 7 in the GC arm and 8 in the DC arm.

DISCUSSION

Adjuvant chemotherapy is now considered to be a standard of care in stage II and III completely resected NSCLC [2].

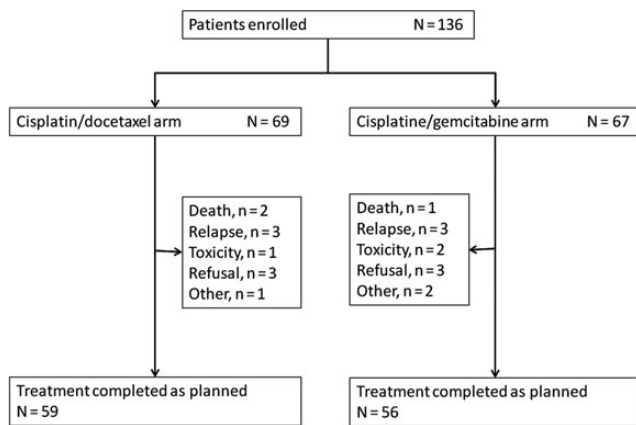


Figure 1: CONSORT flow diagram.

Table 1: Patient characteristics of each treatment arm

	CDDP/GC, n = 67 (%)	CDDP/DC, n = 69 (%)	P-values
Male sex	50 (75)	51 (74)	ns
Age, median (range)	57 [44–74]	57 [36–71]	ns
Stage pIB/II/III	18 (27)/26 (39)/23 (34)	25 (36)/20 (29)/24 (35)	ns
(bi)lobectomy	56 (84)	59 (86)	ns
Pneumonectomy	11 (16)	10 (14)	ns
ADC/SCC/Others	33 (50)/17 (25)/17 (25)	42 (61)/15 (22)/12 (17)	ns
Minor postoperative complications	9 (13)	11 (16)	ns

ADC: adenocarcinoma; SCC: squamous cell carcinoma; GC: gemcitabine; DC: docetaxel; CDDP: cisplatin.

Nonetheless, the optimal regimen has yet to be determined while the VC regimen remains the most widely used and the current trial assessed two other alternative regimens, GC and DC. While the comparison between these regimens with VC would be interesting, the oncological community is now favouring molecular-based or targeted therapy-based adjuvant trials. Therefore, the funding, accrual and adhesion to any large trial comparing two chemotherapy regimens is unlikely, thus reinforcing the need to publish already available data in this setting. The presented data show that GC and DC are feasible adjuvant chemotherapy regimens with good compliance for completely resected NSCLC patients. These regimens translate into comparable outcomes in terms of QoL and efficacy, and show acceptable safety profiles. Despite some reservations stemming from cross-trial comparisons, our study supports the possible use of GC or DC as an adjuvant regimens, especially when considering their QoL impact as compared with the VC regimen.

QoL is a crucial parameter in the assessment of cancer treatment strategies, especially when comparing very similar

therapies. It is however difficult to assess and measure objectively. We used standardized and the well-accepted dedicated EORTC QLQC30 and LC13 questionnaires. As done in most studies dealing with QoL based upon these questionnaires, we looked at absolute values, but did not consider the net changes in score in comparison with the baseline. The 6- to 8-week delay for adjuvant chemotherapy was considered as an inclusion criterion, meaning that none of the patients received adjuvant chemotherapy sooner than 6 weeks and later than 8 weeks after surgery. This clause obviously led to select a subset of fit patients in whom surgery by itself did not impact early QoL that much, because patients having had any significant postoperative complication were not included in the trial. Therefore, the exact time between surgery and start of chemotherapy was not collected nor analysed as a factor potentially affecting QoL in both arms due to this limitation. Another limitation is linked to the multi-institutional design of the study. We can only speculate that patients enrolled in each centre received similar perioperative management, especially for pain control and postoperative rehabilitation, in adherence with current national care guidelines. However, baseline QoL values were not significantly different between treatment arms, thus suggesting similar levels of independence, mobility and freedom from main disabling symptoms. None of the patients in the present study received video-assisted thoracic surgery (VATS) or robot-assisted thoracic surgery (RATS) given that available national guidelines at that time recommended to limit the use of minimally invasive techniques to patients with stage IA NSCLC. Finally, the small size of the overall cohort precluded any sub-group analysis to look at the effect of the adjuvant therapy on QoL according to some relevant characteristics such as the extent of lung resection (lobectomy vs pneumonectomy), histology or pathological stage, age and co-morbidities.

When compared with preoperative status, QoL in patients with resected NSCLC may be adversely affected during 3–6 months following thoracic surgery, with a complete recovery within 6–12 months. Adjuvant chemotherapy may additionally affect QoL for a various length of time [8]. The data reported here suggest that recovery may be delayed, but otherwise not seriously affected, by GC- or DC-based adjuvant chemotherapy. It seems to be also true in elderly patients as reported recently [17]. Interestingly, the QoL was not differentially influenced by the number of infusion, the rate of adverse events, confirming that QoL must be considered by itself. Surprisingly, the fatigue remained stable during the adjuvant chemotherapy maybe as a consequence of chemotherapy while usually improving in the weeks after surgery or an adaptation to a physically compromised condition [18]. In addition, both these regimens might be better tolerated with a lower impact on QoL than the VC regimen [19], to be also compared with the pemetrexed/cisplatin regimen widely used in advanced non-squamous NSCLC and now reported in the adjuvant setting [20]. When selecting and discussing chemotherapy with patients, the short-term and long-term QoL effects of various combinations should be thoroughly addressed and explained so as to encourage patients' active involvement in treatment decisions. Unfortunately, QoL issues are often overlooked.

As shown in previous trials and meta-analyses dedicated to stage IIIB/IV NSCLC patients, GC and DC efficacy rates seem comparable. It should be noted, however, that survival data are

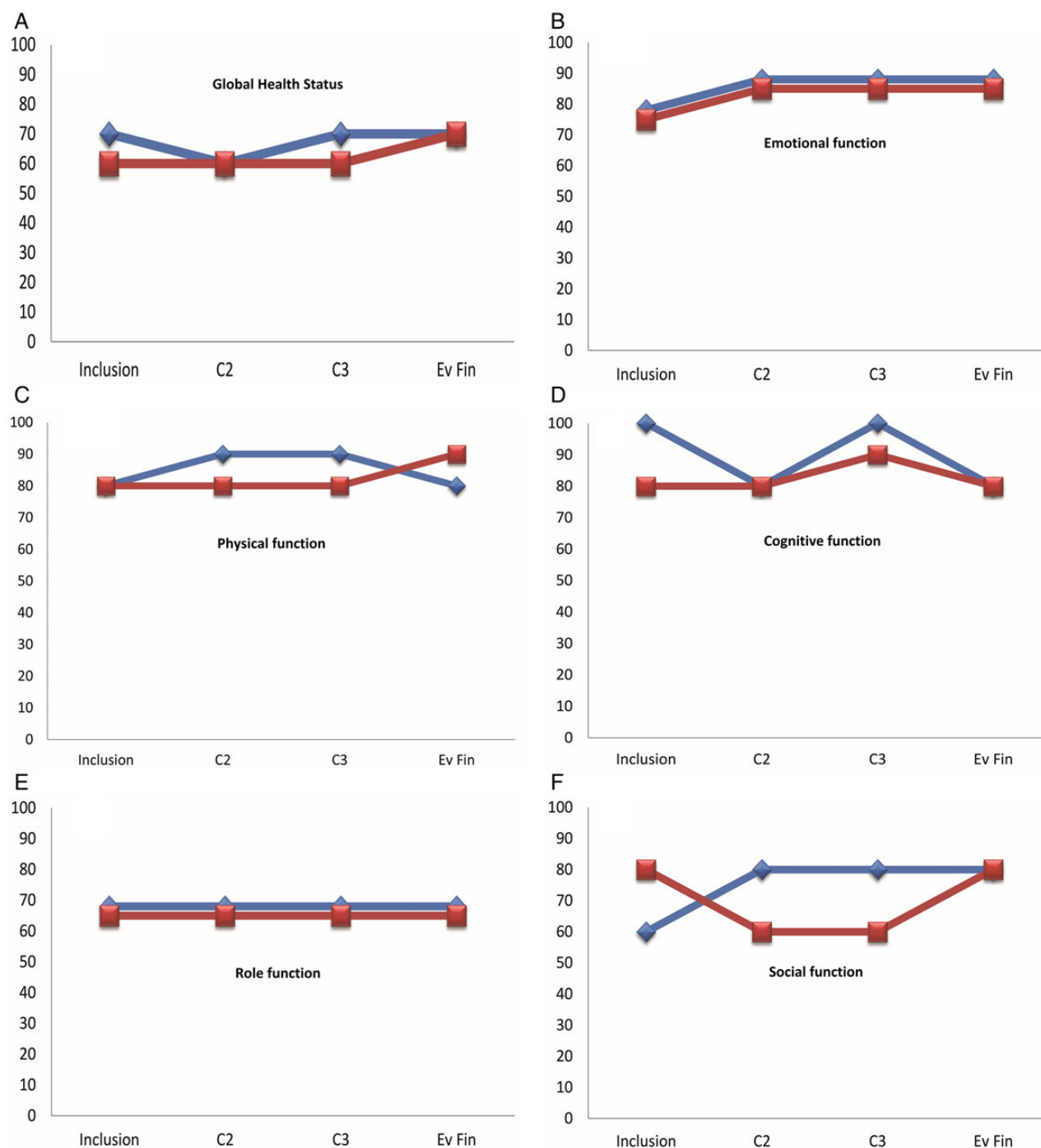


Figure 2: Functional scores of each treatment arm as assessed by the EORTC QLQ-C30 questionnaire. Red: DC arm; blue: GC arm.

to be interpreted with caution giving the number of censored patients. The results reported here might have been influenced by the number of cycles planned in the treatment plan. Indeed, as many perioperative trials designed in the same period [21, 22], three cycles only were planned whereas four cycles of cisplatin-based chemotherapy is now the standard. However, the influence of a difference between GC and DC of one additional cycle on safety and QoL, although possible, is unlikely, given the study design.

Much progress remains to be made. The future of adjuvant chemotherapy will be shaped by individualized treatment strategies based mainly on biological profiling. Useful biomarkers may include excision repair cross-complementation group 1 (ERCC1) for sensitivity to platinum-based therapy [23] or beta-tubulin III for sensitivity to taxanes or vinorelbine [24]. However, individualization will not be possible for all patients, and those unsuited to it may benefit from treatment options eventually based on GC or DC regimens.

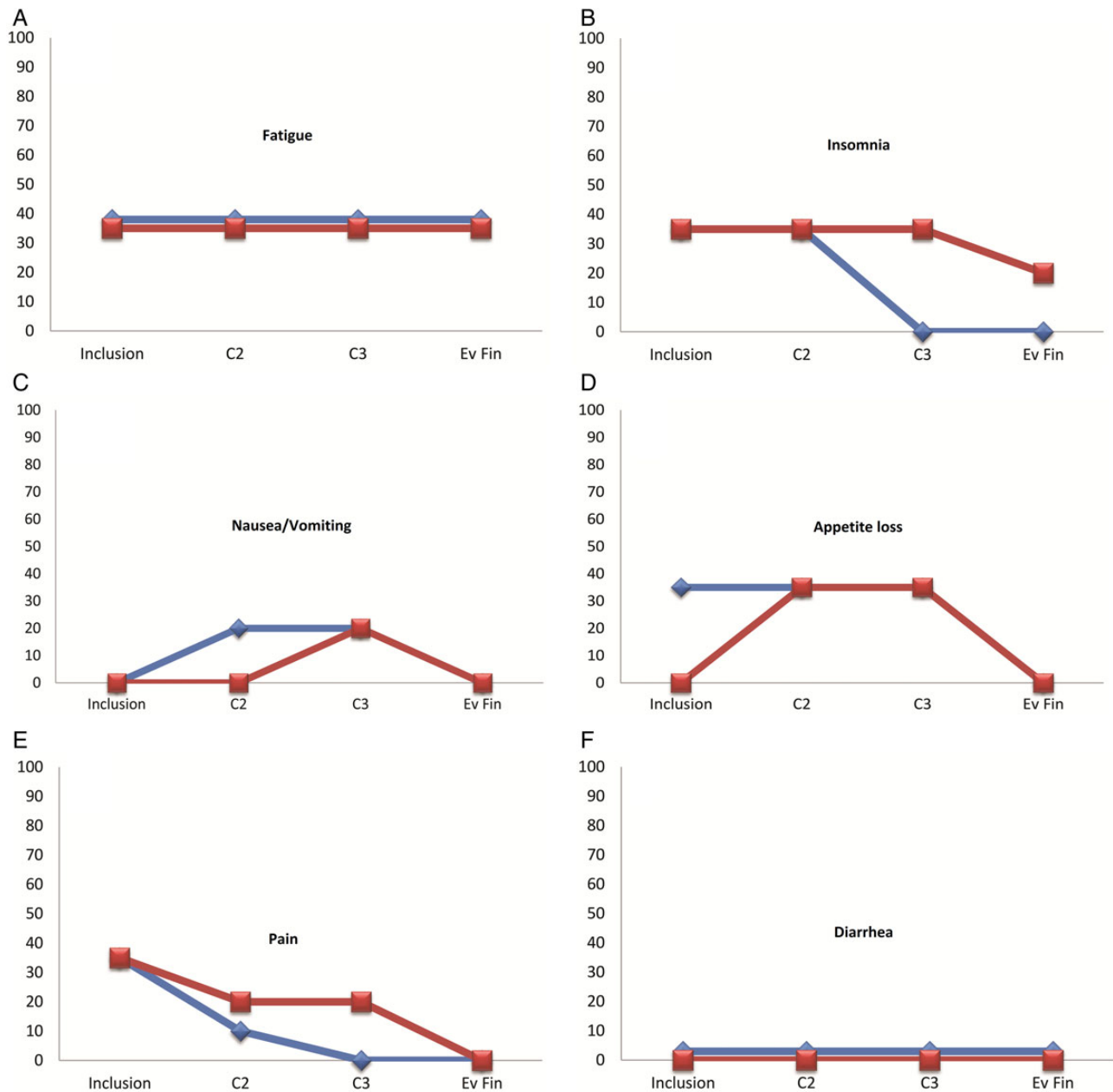


Figure 3: Symptoms scores of each treatment arm as assessed by the EORTC QLQ-C30 questionnaire. Red: DC arm; blue: GC arm.

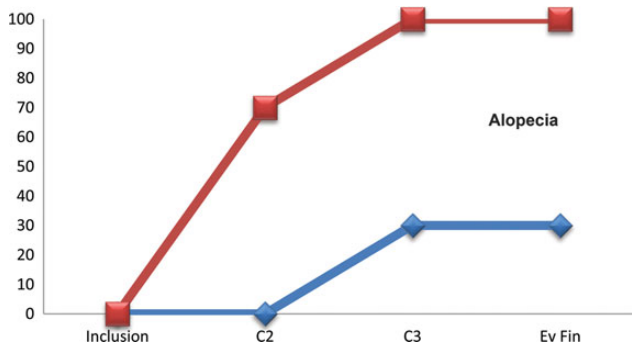


Figure 4: Alopecia of each treatment arm as evaluated by the EORTC LC13 questionnaire. Red: DC arm; blue: GC arm.

In conclusion, DC or GC adjuvant chemotherapy for completely resected NSCLC might be an acceptable alternative to currently recommended combinations and might be compared with the VC regimen. This study did not demonstrate any significant negative QoL impact of DC and GC in resected lung cancer patients, and might be useful when discussing treatment options with such patients.

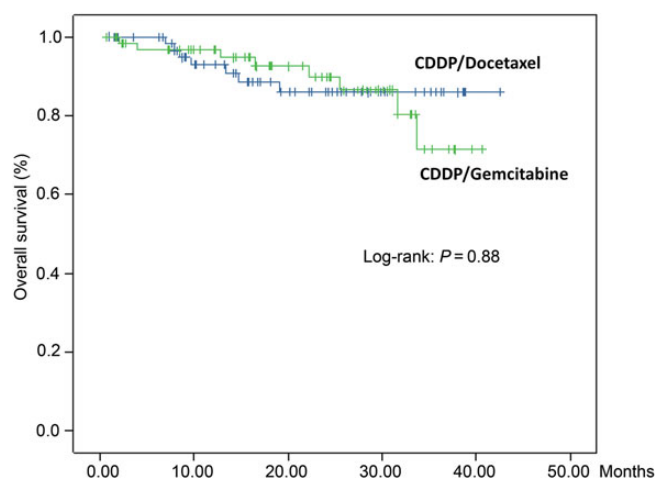
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Table 2: Summary of Grade 3/4 toxicities of each treatment arm

GR 3-4 toxicities	CDDP/GC n = 67 (%)	CDDP/DC n = 69 (%)	P-values
Haematological (global)	22 (32.8)	15 (21.7)	0.15
Anaemia	1 (1.5)	0 (0.0)	0.49
Neutropenia	19 (28.4)	15 (21.7)	0.37
Thrombopenia	6 (9.0)	1 (1.4)	0.06
Non-haematological (global)	22 (32.8)	18 (26.1)	0.39
Asthenia	5 (7.5)	5 (7.2)	1.00
Nausea/vomiting	7 (10.4)	5 (7.2)	0.51
Infection	2 (3.0)	1 (1.4)	0.62
Neuropathy	0 (0.0)	1 (1.4)	1.00
Alopecia	2 (3.0)	9 (13.0)	0.03

CDDP: cisplatin; GC: gemcitabine; DC: docetaxel.

**Figure 5:** Kaplan-Meier overall survival figures according to treatment arms.

Tchouhadjian, Philippe Astoul, Christophe Doddoli (Marseille), Mariette Baud (Saint Antoine, Paris), Henri Berard, Jean-Baptiste Roseau, Gilbert Nguyen (HIA Sainte-Anne, Toulon), Boris Melloni, Francis Touraine, François Bonnaud (Limoges). Much appreciation also goes out *in memoriam* to Thierry Slacmeuld, who strongly believed in this project and continuously supported it.

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