Review

Ifosfamide in non-small-cell lung cancer

R. Rosell, C. Martin & C. Balaña
Medical Oncology Service, University Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

Summary

Ifosfamide has been used in combination with several drugs including cisplatin, giving rise to multiple doublets and triplets including the ifosfamide–cisplatin–mitomycin regimen (Cullen’s MIC regimen) that has been commonly used in Europe. However, new combinations are challenging the activity of the old chemotherapy regimens, especially in terms of objective response rate and time to progressive disease, as has been shown in several phase III randomized trials. Among these new combinations, ifosfamide–vinorelbine and ifosfamide–gemcitabine–cisplatin are especially promising. In this paper, several ifosfamide doublets and triplets are reviewed.

Key words: doublets, ifosfamide, non-small-cell lung cancer, triplets

Introduction

While some advances have been made in the clinical management of NSCLC, still only 13% of newly diagnosed patients will survive more than five years. We have demonstrated that hematogenic tumor cell dissemination is a frequent and early event in NSCLC [1]. Also, we know that chemotherapy produces predictable and reproducible responses in stage IV NSCLC and an objective response rate (OR) of 15% in multiple single-agent phase II trials, which is considered the threshold of clinical usefulness. Before 1990, only five antineoplastic agents were considered active: cisplatin, ifosfamide, mitomycin, vinblastine and vindesine. A variety of new active drugs has since appeared, offering the possibility of choosing from many multiple-drug combinations and posing the questions of which regimen is more efficacious and whether pentaplets are better than doublets or triplets without adding detrimental toxicity. We must also consider problems such as sequence-dependent hematological toxicity, which has been associated with the paclitaxel–cyclophosphamide doublet [2].

However, survival time can be improved with these regimens. Cullen’s impeccable study [3], in which 797 NSCLC patients were randomized, showed a significant (P = 0.02) positive effect of mitomycin–ifosfamide–cisplatin (MIC) chemotherapy on survival and proved that a meta-analytical review of chemotherapy is not necessary when a large-scale trial is well designed. Such an analysis had previously shown an increase of 1.5 months in median survival, with a 10% absolute increase at 1 year [4]. A recent randomized trial indicated that the addition of paclitaxel to cisplatin may lead to a two-month improvement in survival [5]. Two other randomized trials were able to demonstrate an improvement in survival related to a specific chemotherapy regimen.

Le Chevalier et al. [6] showed a higher response rate and increased survival with a cisplatin–vinorelbine combination than with cisplatin–vindesine or with vinorelbine alone. Also, a multicenter Italian trial found a benefit in terms of response rate and median survival time with triplets of either MIC or mitomycin–vindesine–cisplatin over the cisplatin–etoposide doublet [7].

Single-agent ifosfamide in NSCLC

Ifosfamide is an alkylating agent that produces responses of over 20% in patients with advanced NSCLC [8, 9]. Data pooling carried out by us [10] showed that the activity of ifosfamide as a single agent in NSCLC was 17% in more than 500 patients, which is similar to that reported for cisplatin. In a Southwest Oncology Group study [11], ifosfamide had a 9% OR in 113 patients with extensive NSCLC, whereas other authors have claimed up to a 32% OR [12]. In any case, the activity of ifosfamide is consistent whether the administration schedule is fractionated or bolus. The main criticism of single-agent ifosfamide studies stems from the fact that these early studies were carried out at a time when there were no rigorous rules for phase II studies; hence, the validity of ifosfamide’s reported activity needs to be reconfirmed.

Classical ifosfamide combinations

Cyclophosphamide–ifosfamide combinations

Thatcher et al. [13] treated 45 patients with the two alkylating agents, proving that both agents have different interactions at the DNA level, have no cross-resistance.
clinically, and also have different toxicity patterns. Myelo-suppression is the cyclophosphamide dose-limiting toxicity, with encephalopathy being the most important potential problem with ifosfamide. A 38% OR was obtained, with 7% complete response and tolerable toxicity. Cisplatin-based regimens have been the backbone of most clinical trials in NSCLC; however, the use of high-dose cisplatin did not portend a reliable response rate. This prompted us to use cyclophosphamide 2.5 g/m² and ifosfamide 3.5 g/m² as preoperative chemotherapy in stage IIIA and IIIB patients, with mesna 12 g/m² given additionally to prevent drug hematuria. Six of twenty-three patients (26%) had OR. Time to progression was seven months. After 52 cycles, cyclophosphamide–ifosfamide doses were cut down, as 8 of 16 patients required hospitalization for fever during neutropenia nadirs [10].

Ifosfamide triplets

Girón et al. [14] obtained a 67% OR in 32 stage III & IV patients with a MIC regimen. In their seminal study using MIC, Cullen et al. [15] obtained a 56% OR in 66 patients evaluable for response with seven patients (11%) attaining complete response. Antón et al. [16], also using MIC at higher cisplatin (80 mg/m²) and mitomycin (10 mg/m²) doses, attained a similar OR of 56%. Data pooling of MIC regimen studies showed a 42% OR among 396 patients [10]. Ifosfamide triplets have been extensively reviewed elsewhere [9]. We [17] also performed a randomized study comparing vindesine–cisplatin–mitomycin (MVP) with vindesine–cisplatin–ifosfamide (IVP) in patients with advanced NSCLC. The OR was 26% in the MVP arm and 20% in the IVP. More nephrotoxicity was produced in the MVP arm. Similar results were obtained by other investigators and are shown in Table 4 of the detailed Eberhardt and Niederle Review [9]. We used [18] Cullen’s MIC regimen as preoperative chemotherapy in a randomized trial, obtaining a 60% OR; more importantly, the risk of death in the surgery group was five times that in the MIC plus surgery group. At the time of seven-year follow-up, differences still remained; median survival for the MIC chemotherapy group was 22 months (95% CI: 13.5–30.5 months), and for the surgery group, it was 10 months (95% CI: 7.4–12.5 months, P = 0.002 by log-rank test). Recently, we have tested whether higher cisplatin doses in the MIC regimen are capable of increasing complete pathologic responses. To date, 83 patients have been entered in this Spanish Lung Cancer Group (SLCG) trial, and although differences have been noted in radiographic OR, no differences in survival have been seen [19].

Other new ifosfamide combinations

Ifosfamide–paclitaxel

This combination at a dose of 3–5 g/m² has been tested in a total of 141 patients. The OR ranges from 21%–34%, and median survival, when available, does not reach 40 weeks [20, 21].

Ifosfamide–paclitaxel–cisplatin

Palladchahry [22] administered ifosfamide 3 g/m² on days 1 and 2, paclitaxel 135–175 mg/m² on day 2, and carboplatin AUC of 5 and granulocyte-colony stimulating factor (G-CSF) starting on day 4. Grade 4 neutropenia was frequently observed. Four patients achieved complete response and six achieved partial response for an overall OR of 100%. Other investigators have used this triplet; however, myelosuppression is severe, mainly when prolonged infusion for paclitaxel is used.

Ifosfamide–paclitaxel–etoposide–carboplatin

Two studies [23, 24] have used carboplatin 300 mg/m², ifosfamide and etoposide on days 1, 2 and 3 and paclitaxel 120–175 mg/m² on day 4. G-CSF was given to all patients. The Strauss et al. [23] trial reported a 32% OR, and 26% of patients had febrile neutropenia. It seems that triplets or quadruplets are not superior to doublets. Also a sequence-dependent hematological toxicity has been observed with the paclitaxel–cyclophosphamide doublet that is more severe in cycles where paclitaxel is administered first [2].

Ifosfamide–vinorelbine

At the University of Chicago [25], ifosfamide 1.6 g/m² (one-hour infusion) on days 1, 2 and 3 and vinorelbine 30 mg/m² on three consecutive days plus G-CSF on days 5–11 was used. The overall OR was 40%, median survival was 50 weeks, and one-year survival was 48%.

Ifosfamide–gemcitabine combinations

Recchia et al. [26] gave ifosfamide 1.5 g/m² on days 1–3, gemcitabine 500–1000 mg/m² and vinorelbine 25 mg/m² on days 3 and 8; a 40% OR was observed. Manegold et al. [27] tested gemcitabine 1000 mg/m² on days 1, 8 and 15 and ifosfamide 1.5 g/m² on days 8–12 every four weeks, obtaining a 32% OR. Cisplatin–ifosfamide–gemcitabine has been tested in Spain in several small studies [28–30]. Barneto et al. [28] used cisplatin 50 mg/m², ifosfamide 3 g/m² and gemcitabine 1000 mg/m² on days 1 and 8 every 21 days; interim results yielded a 33% OR without significant toxicity. Mohedano et al. [29] used gemcitabine 1000 mg/m² on days 1 and 8, cisplatin 80 mg/m² on day 2 and ifosfamide 3.5 g/m² on day 2, obtaining a 60% OR. Finally Vadell et al. [30] used gemcitabine 1000 mg/m² on days 1 and 8, ifosfa-
mide $3 \text{ g/m}^2$ and cisplatin $50 \text{ mg/m}^2$ on day 1, which also proved to be an active regimen.

Conclusions

Based on the above data, on the superior activity of gemcitabine/cisplatin compared to cisplatin–etoposide (41% vs. 22%, $P = 0.02$) found in a SLGC study [31], and on the longer time to progression with gemcitabine–cisplatin compared to cisplatin–etoposide (median of 6.9 months versus 4.3 months, $P = 0.01$ by log-rank test) found in the same study, the SLGC has designed a large three-arm randomized trial in which 600 stage IV patients will be randomized to receive either cisplatin–gemcitabine or cisplatin–gemcitabine–vinorelbine or vinorelbine–gemcitabine for three cycles and then vinorelbine–ifosfamide for three cycles. The main aim of this study is to compare the survival of patients treated with a gemcitabine–cisplatin doublet versus a triplet versus sequential administration of two doublets without cisplatin.

In summary, this diversity of new drugs poses the dilemma of deciding which is the most effective first-line chemotherapy combination, whether triplets or quadruplets are better than doublets, and whether sequential chemotherapy could still improve response rate and survival. The role of ifosfamide in this chemotherapy puzzle needs to be elucidated.

Acknowledgements

We would like to thank M. Balcells, MD, of Prasfarma, Barcelona, Spain for technical assistance and M. M. Cullen, MD, from University Hospital Birmingham, UK for allowing us to review unpublished material.

References

19. Felip E, Moreno I, Canela M et al. Spanish Lung Cancer Group randomized trial of preoperative chemotherapy (cisplatin either 50 mg/m² or 100 mg/m²) in stage IIIA non-small-cell lung cancer. Lung Cancer 1997; 18 (Suppl 1): 64 (Abstr 243).


Correspondence to:
R. Rosell, MD, PhD
Medical Oncology Service
University Hospital Germans Trias i Pujol
Ctra Canyet s/n.
08916 Badalona, Barcelona
Spain
E-mail: rrosell@ns.hugtip.scs.es