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REVIEW

Gemcitabine for the treatment of advanced nonsmall cell lung cancer

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Abstract: Gemcitabine is a pyrimidine nucleoside antimetabolite agent which is active in several human malignancies, including nonsmall cell lung cancer (NSCLC). Because of its acceptable toxicity profile, with myelosuppression being the most common adverse event, gemcitabine can be safely combined with a number of cytotoxic agents, including platinum derivatives and new-generation anticancer compounds. In fact, the combination of gemcitabine and cisplatin is a first-line treatment for patients with advanced NSCLC, pharmacoeconomic data indicating that it represents the most cost-effective regimen among platinum-based combinations with third-generation cytotoxic drugs. The drug has been investigated in the context of nonplatinum-based regimens in a number of prospective clinical trials, and might provide a suitable alternative for patients with contraindications to platinum. Recently, gemcitabine-based doublets have been successfully tested in association with novel targeted agents with encouraging results, providing further evidence for the role of the drug in the treatment of NSCLC. In the last few years several attempts have been pursued in order to identify molecular predictors of gemcitabine activity, and recent data support the feasibility of genomic-based approaches to customize treatment with the ultimate goal of improving patient outcome.

Keywords: gemcitabine, chemotherapy, pharmacoeconomics, nonsmall cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death in both men and women worldwide, thus representing a major healthcare issue.[1] Nonsmall cell lung cancer (NSCLC) accounts for the vast majority of the cases, adenocarcinoma and squamous cell carcinoma being the most frequent histotypes. Although recent advances in the knowledge of lung cancer biology led to the development of new effective targeted agents directed against pathways that are selectively activated in cancer, platinum-based chemotherapy remains the mainstay of treatment for unselected patients with advanced disease.[2] Among third-generation cytotoxic compounds, gemcitabine, a pyrimidine nucleoside antimetabolite, has been demonstrated to be one of the most effective agents, particularly when administered in combination regimens.

Compound characteristics

Mechanism of action

Gemcitabine (2′deoxy-2′2′-difluorocytidine monohydrochloride), is a potent and specific pyrimidine nucleoside antimetabolite which is structurally analogous to deoxycytidine. Due to its hydrophilic nature, the drug requires to be actively introduced into the cells through highly specialized carriers, including the human equilibrative nucleoside

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transporter-1 (hENT1) and, to a lesser extent, the human concentrative nucleoside transporter-1 and -3 (hCNT-1, hCNT-3).[3] On uptake into the cells, gemcitabine can be either deaminated to an inactive form, 2′, 2′-difluorodeoxyuridine (dFdU) by cytidine deaminase (CDA), or phosphorylated by deoxycytidine kinase (dCK) to dFdC-5′-monophosphate (dFdCMP) and to the active metabolites diphosphate and triphosphate.[4] While dFdC-5′-diphosphate can inhibit ribonucleotide reductase (RR), an enzyme essential for the production of deoxyribonucleotides prior to DNA synthesis in S phase of dividing cells, dFdC-5′-triphosphate is incorporated into DNA resulting in early termination of DNA synthesis.[4]

Toxicity

Gemcitabine has an extremely favorable toxicity profile, a feature that has prompted the investigation of the agent in combination with other cytotoxic compounds. Myelosuppression represents the main dose-limiting toxicity and occurs in approximately two-thirds of the patients that receive the drug as single agent over a standard 30-minute infusion, about 25% of individuals experiencing grade 3 and 4 neutropenia.[5] Nevertheless, <1% of the patients require treatment discontinuation for hematologic toxicity, while red blood cell transfusions can be necessary in up to 20% of the patients, according to pancreatic cancer studies.[5] Other commonly observed adverse events include gastrointestinal toxicity, mild to moderate nausea and vomiting being reported in about 70% of patients, and transient elevation of serum transaminases in 70%, but with no evidence of increasing hepatic toxicity with either longer duration of exposure to the drug or with greater total cumulative dose.[5] In addition, gemcitabine might cause mild proteinuria (45%) and hematuria (35%), fever (40%), and rash (30%).[5]

Dosage

Gemcitabine is commonly administered weekly at 1000 or 1250 mg/m^2 as a 30-minute intravenous infusion for 2 or 3 weeks followed by a week of rest. This schedule seems to provide the best compromise in terms of toxicity and dose intensity in NSCLC patients.[6] In fact, deoxycitidine kinase is saturated at plasma concentrations achieved after a 30-minute infusion.[7,8] However, the optimal plasma drug concentration that maximizes the rate of formation of gemcitabine triphosphate is 20 μmol/Lμ, a target value that can be achieved with dose rates of about 10 mg/m^2/min (prolonged infusion), according to phase I trials.[7,8] For this reason, accumulation of higher intracellular gemcitabine triphosphate concentration, which may result in enhanced cytotoxic activity, can be reached by prolonged infusion rates rather than increased drug dose. This hypothesis has been tested in a number of phase II randomized studies with gemcitabine administered either as single agent or in combination with cisplatin, producing conflicting results.[9–11] Because of the lack of clear superiority in terms of activity and/or toxicity favoring the prolonged infusion rate, a 30-minute infusion schedule should remain the standard modality for gemcitabine administration in patients with advanced NSCLC.

Gemcitabine in platinum-based combinations

Platinum-based chemotherapy has been shown for almost 15 years to significantly improve survival and quality of life in patients with advanced NSCLC.[12] Since its early development gemcitabine has emerged as an ideal partner for platinum compounds, because of its theoretical ability of interfering with the inhibition of repair of platinum-induced DNA damage. Based on the results of several phase III trials,[13–17] gemcitabine in combination with cisplatin now represents a commonly used first-line treatment for patients with advanced NSCLC, particularly in Europe.

At least three phase III studies compared a gemcitabine/cisplatin regimen (GC) with first-generation cisplatin-based combinations or cisplatin alone in the first line setting.[13–15] The Italian Lung Cancer Project investigated the role of the GC regimen in comparison with mitomycin/ifosfamide/cisplatin (MIC) in 307 advanced NSCLC patients.[13] Subjects in the GC arm experienced a significantly higher response rate (38% vs 26%, $P = 0.02$) with no difference in survival and quality of life as compared with the old-generation regimen. The two treatments showed different toxicity profiles. In fact, grade 3 and 4 thrombocytopenia was significantly worse in the GC arm (64% vs 28%, $P < 0.001$), whereas grade 3 and 4 alopecia was observed more commonly in the MIC arm (39% vs 12%, $P < 0.001$). Further evidence in favour of a role for gemcitabine in this setting came from two additional phase III trials. In the Spanish study, 135 patients with advanced disease were randomly assigned to cisplatin with etoposide or gemcitabine.[14] Despite the lack of a survival benefit, patients treated in the experimental arm reported a significantly higher response rate (40.6% vs 21.9%, $P = 0.02$) and time to progression (6.9 vs 4.3 months, $P = 0.01$), with an overall similar toxicity profile. In the study performed by the Hoosier Oncology Group, the association of gemcitabine and cisplatin has been compared with cisplatin single-agent as first line treatment in 522 advanced NSCLC patients.[15]

The GC arm produced a significant improvement over single-agent cisplatin with regard to response rate (30.4% vs 11.1%, $P < 0.0001$), median time to progression (5.6 vs 3.7 months, $P = 0.0013$), and overall survival (9.1 vs 7.6 months, $P = 0.004$), despite a higher incidence of adverse events, mainly hematological.

Due to the development of multiple third-generation cytotoxic agents that can be safely and effectively incorporated in platinum-based regimens, phase III studies have tried to identify whether one combination is superior to the others in terms of activity and toxicity profile[16–18] (Table 1). The Eastern Cooperative Oncology Group (ECOG) randomized 1207 patients to either a reference arm of paclitaxel/cisplatin (PC) or one of three experimental arms, including GC, docetaxel/cisplatin (DC) or paclitaxel/carboplatin (PCb).[16] None of the four regimens exhibited superior response rate or survival, while patients in the GC arm experienced a significantly longer time to progression when compared with those in the reference arm (4.2 vs 3.4 months, $P = 0.001$). Similar results were reported by the Italian Lung Cancer Project trial, where 612 patients with advanced NSCLC were randomly allocated to GC, PCb or vinorelbine/cisplatin (VC).[17] Again, all the regimens showed comparable activity in terms of response rate, time to progression and overall survival. More recently, the GC regimen has been chosen as a reference arm to be compared with an experimental pemetrexed/cisplatin (PmC) combination in 1725 chemonaive patients.[18] While the study met its primary end point of noninferior survival for the PmC over the GC arm, GC produced a significantly longer overall survival in the subgroup of patients with squamous cell histology. This retrospective finding suggests that clinically-selected subsets of patients might derive a substantial benefit from platinum-based combinations including gemcitabine.

Table 1 Phase III trials comparing new generation platinum-based doublets

Trial	Regimens	N	RR (%)	OS (months)	P[a]
ECOG E1594[16]	PC	292	21	7.8	NS[b]
	GC	288	21	8.1	
	DC	293	17	7.4	
	PCb	299	15	8.1	
ILCP[17]	VC	203	30	9.5	NS[c]
	GC	205	30	9.8	
	PCb	204	32	9.9	
H3E-MC-JMDB[18]	GC	863	28.2	10.3	NS
	PmC	862	30.6	10.3	

[a]related to overall survival. [b]PC versus each other regimen. [c]VC versus each other regimen.

Abbreviations: ECOG, East Cooperative Oncology Group; ILCP, Italian Lung Cancer Project; C, cisplatin; Cb, carboplatin; D, docetaxel; G, gemcitabine; P, paclitaxel; Pm, pemetrexed; V, vinorelbine; RR, response rate; OS, overall survival; NS, not significant.

Pharmacoeconomic considerations

The similar activity of new generation platinum-based regimens observed in phase III trials prompted investigators to analyze cost-effectiveness parameters to better identify an optimal combination for the first-line treatment of advanced NSCLC. Two different pharmacoeconomic evaluations performed in the context of the ECOG trial showed that the association of cisplatin and gemcitabine was associated with the lowest total treatment-related costs when directly compared with the two paclitaxel-containing regimens, mostly due to the higher costs of chemotherapy in the PC arm.[19,20] Total costs were similar in the GC and DC arm in Germany, France and in the UK, whereas the GC regimen was associated with lower total costs in Spain and Italy over the docetaxel arm.[19] Overall, these data indicate that the GC regimen was associated with lower total costs than VC, PC and PCb, and similar costs when compared with DC regimen. PCb, which is commonly used as a first-line treatment in the US, has emerged as the most costly regimen in this study, primarily due to the greater acquisition cost of carboplatin as compared with cisplatin.

Novello et al conducted a cost-minimization assessment aimed at comparing the GC, PCb and VC regimens in the study by the Italian Lung Cancer Project.[21] Total treatment-related costs were lower for the GC regimen over PCb and VC combinations. Drug acquisition represented a major determinant of total cost particularly for the PCb regimen, and thus representing the predominant factor responsible for the higher cost of this combination. On the other hand, the median cost saving favoring GC over VC was predominantly due to the higher hospitalization costs in the vinorelbine arm.

Pimentel et al have recently published a pharmacoeconomic evaluation of five platinum-based combinations from the perspective of the Portuguese National Health Service, pooling data from the ECOG and Italian Lung Cancer Project trials.[22] Consistent with previous observations, the authors confirmed the favorable economic impact of the GC combination when compared with the other regimes. Taken together, these data suggest the association of gemcitabine and cisplatin represents a cost-effective option for the first-line treatment of advanced NSCLC patients.

Gemcitabine in nonplatinum-based combinations

Toxicity issues related to the administration of cisplatin led investigators to explore the role of combinations of third generation cytotoxic agents in nonplatinum-based regimens, with gemcitabine being one of the most investigated drugs. Several compounds have been associated with gemcitabine, including vinorelbine and, above all, taxanes (Table 2). Italian investigators performed a phase III trial aimed at comparing gemcitabine/vinorelbine (GV) with either VC or GC.[23] Patients allocated in the cisplatin-based arms had a significantly longer progression-free survival (23 vs 17 weeks, $P = 0.004$) and a trend toward improved survival (38 vs 32 weeks, $P = 0.08$), albeit comparable response rate and worse toxicity. Two additional studies, however, showed that the association of gemcitabine and vinorelbine can compare well with platinum-based treatments.[24,25] In fact, German and Swiss investigators reported neither overall nor event-free survival difference when comparing a GV combination with an unconventional gemcitabine/vinorelbine/cisplatin triplet.[24] More recently, a Japanese phase III trial compared a GV regimen followed by docetaxel with PCb in 401 patients with advanced disease.[25]

Table 2 Phase III trials comparing new generation nonplatinum-based with platinum-based regimens

Trial	Regimens	N	RR (%)	OS (months)	p[a]
Gridelli[23]	GC	250	30	8.9	NS
	VC				
	GV	251	25	7.5	
Laack[24]	GVC	144	28.3[b]	7.6	NS
	GV	143	13.0	8.4	
Kubota[25]	PCb	197	37[b]	14.1	NS
	GV → D	196	25	13.6	
Georgoulias[26]	VC	192	39	9.7	NS
	GD	197	30	9.0	
Pujol[28]	VC	156	36	9.6	NS
	GD	155	31	11.1	
Kosmidis[29]	PCb	252	28	10.4	NS
	GP	257	35	9.8	
Kosmidis[30]	GCb	227	27	10.5	NS
	GP	225	31	10.0	
Smit[31]	PC	159	32	8.1	NS[c]
	GC	160	37	8.9	
	GP	161	28	6.7	

[a]related to overall survival. [b]significantly higher. [c]PC versus each other regimen.
Abbreviations: C, cisplatin; Cb, carboplatin; D, docetaxel; G, gemcitabine; P, paclitaxel; V, vinorelbine; RR, response rate; OS, overall survival; NS, not significant.

Despite a significantly higher response rate for patients who received PCb (37% vs 25%, $P = 0.012$), the two arms had comparable overall and progression-free survival, indicating that this strategy might be a suitable alternative for patients with contraindications to platinum.

The association of gemcitabine and docetaxel (GD) has been explored by Greek investigators in two phase III trials in untreated NSCLC patients.[26,27] Particularly, in the first published study, the GD arm showed similar activity compared with a standard VC regimen, but with a significantly better toxicity profile.[26] Similar results emerged from a French trial conducted in 311 untreated patients,[28] thus confirming the activity of the regimen and its favorable toxicity profile. More data are now available for the association of gemcitabine and paclitaxel (GP), which has been extensively characterized in at least three phase III studies enrolling more than 1500 patients.[29–31] The new regimen showed comparable activity and toxicity with carboplatin-based combinations, but a trend towards lower efficacy compared with cisplatin-containing doublets, raising concerns about its applicability in clinical practice. Nevertheless, it should be noted that a meta-analysis performed to address the role of nonplatinum chemotherapy in the first-line treatment of advanced NSCLC reported no difference in 1-year survival between platinum-doublets and nonplatinum regimens with third-generation agents, leaving space for further development of platinum-free strategies in the first-line setting.[32]

Gemcitabine in elderly patients

Given the toxicity generally associated with conventional chemotherapy and the modest survival advantage obtained with cytotoxic agents, the role of systemic treatments for elderly patients has been under debate for years. A review of 2531 patients treated by SWOG investigators for advanced NSCLC between 1974 and 1988 showed that age over 70 years represents an independent predictor of improved survival.[33] In addition, another retrospective study performed to assess the tolerance of chemotherapy in elderly patients enrolled in phase II trials showed no difference in outcome between younger and older subjects with a cut-off of 65 years.[34] The ELVIS trial, a randomized phase III study of vinorelbine vs best supportive care, provided the first compelling evidence that elderly patients can derive a substantial benefit from chemotherapy.[35] The results from this study encouraged the investigation of other third-generation cytotoxic agents in this setting. Gemcitabine single agent has been tested in multiple phase II trials with response rates up to 38% and median survival up to 9 months in

patients over 70 years of age.[36–38] To optimize the activity of single-agent schedules, gemcitabine has been combined with different partners, including vinorelbine and taxanes. Investigators from the Southern Italy Cooperative Oncology Group conducted a phase III study to assess whether the addition of gemcitabine to vinorelbine could lead to improved outcome over vinorelbine alone in patients with advanced NSCLC ≥ 70 years of age.[39] An interim analysis led to an early termination of the study due to the clear advantage favoring the combination arm in terms of reduced risk of death (HR 0.48, $P < 0.01$). However, the poor outcome for patients in the single agent arm was not comparable with historical controls, thus precluding any firm conclusion. Moreover, in the larger MILES trial of GV vs gemcitabine vs vinorelbine the combination arm was not associated with improved outcome but rather with increased toxicity discouraging the introduction of this regimen in clinical practice.[40]

The association of gemcitabine and taxanes has been extensively studied in phase II trials with response rates averaging approximately 30%.[41–44] A pooled analysis of six clinical trials conducted by the Hellenic Oncology Research Group showed comparable efficacy and toxicity of GD combinations between younger (<70 years) and older (≥70 years) patients.[45] However, a recently published phase III trial of GD vs docetaxel alone in elderly patients and subjects with poor performance status showed no survival improvement for the combination arm, suggesting that single agent chemotherapy should remain the standard of care for these groups of patients.[46]

In the attempt to shed some light on gemcitabine-based doublets vs single-agent therapy for elderly patients with advanced NSCLC, Italian investigators have recently published a literature-based metanalysis pooling data from four phase III trials.[47] The authors observed a significant difference in terms of response rate favoring gemcitabine-based doublets with a trend toward improved 1-year survival. Toxicities were comparable, except for increased grade 3 and 4 thrombocytopenia for patients treated with doublets. Overall, these findings address the need for further prospective studies to identify the optimal role for nonplatinum-based treatments in this setting.

Gemcitabine in association with targeted agents

Recent advances in the molecular knowledge of cancer led to the development of targeted agents aimed at disrupting pathways that are essential for the survival and progression of human malignancies. In the last few years a multitude of new compounds has been tested either alone or in association with conventional chemotherapy with the ultimate goal of improving the outcome of patients with advanced NSCLC. The Epidermal Growth Factor Receptor (EGFR) has been one of the most attractive and investigated targets, because of its common overexpression in NSCLC. Erlotinib and gefitinib, two orally available EGFR tyrosine kinase inhibitors, showed encouraging activity as single agents in unselected patients with advanced NSCLC treated in the context of phase II studies.[48–51] Nevertheless, only erlotinib was able to offer a significant survival advantage over best supportive care in pretreated unselected patients,[52] with subsequent approval by regulatory agencies in several countries. Four large phase III randomized trials were performed to ascertain whether the addition of either erlotinib or gefitinib to standard first line chemotherapy, including gemcitabine and cisplatin, could improve survival in untreated NSCLC.[53–56] Disappointingly, all these studies failed to meet their primary endpoint, possibly due to the lack of patient selection. In fact, it is currently known that EGFR tyrosine kinase inhibitors are particularly active in patients harboring EGFR tyrosine kinase domain mutations and/or EGFR gene gain.[57–59] Whether the addition of chemotherapy to EGFR tyrosine kinase inhibitors in biologically selected patients might provide any further benefit is as yet unknown and prospective trials addressing this issue are warranted.

Other anti-EGFR strategies include the use of monoclonal antibodies directed against the extracellular domain of the protein, such as cetuximab. In a phase III trial of VC with or without cetuximab in EGFR overexpressing NSCLC, patients allocated in the experimental arm experienced significantly longer survival, a finding that might substantially impact on the treatment strategies for chemonaive patients.[60] The drug has been also studied in association with gemcitabine/platinum-based doublets in a randomized phase II trial.[61] Interestingly, EGFR overexpression at immunohistochemistry was not an inclusion criterion. The noncomparative nature of the trial precludes any firm conclusion, but it should be noted that patients who received cetuximab had better response rate, progression-free survival and overall survival, suggesting that cetuximab might synergize with gemcitabine/platinum doublets and be responsible for the observed improved outcome.

More recently, inhibition of angiogenesis has emerged as a potentially effective strategy in controlling tumor growth.[62] Bevacizumab, an anti-VEGF monoclonal antibody, has been shown to increase survival when added to a standard PCb regimen in patients with advanced nonsquamous NSCLC and

no brain metastases in a large phase III trial.[63] Nevertheless, the addition of bevacizumab has been significantly associated with greater grade 3 and 4 toxicity and with more treatment-related deaths, possibly because of the dose used (15 mg/kg on day 1 every 3 weeks). The agent has been also tested in combination with GC in a recently published phase III study.[64] In the AVAil trial 1043 patients with nonsquamous NSCLC and lack of brain metastases were randomly assigned to GC alone vs GC plus low-dose bevacizumab (7.5 mg/kg) or GC plus high-dose bevacizumab (15 mg/kg). The primary endpoint has been amended from overall survival to progression-free survival. The trial confirmed the activity of bevacizumab in this group of patients, with significantly prolonged progression-free survival in both the experimental arms (HR 0.75, $P = 0.003$ and HR 0.82, $P = 0.03$ for low- and high-dose vs placebo, respectively). Importantly, the addition of bevacizumab was not associated with a greater incidence of grade 3 or 4 adverse events, suggesting that gemcitabine and cisplatin represent effective and safe partners for this agent.

Pharmacogenomic approaches to gemcitabine-based chemotherapy

The improvement of molecular biology techniques has helped to better elucidate the mechanism of action of cytotoxic agents and has led to the identification of markers related to sensitivity or resistance to specific compounds, ultimately contributing to the concept of customized chemotherapy. In fact, it has been hypothesized that the evaluation of multiple biomarkers on tumor tissue might help to select the optimal cytotoxic treatment for each patient.

A number of molecular predictors of gemcitabine activity have been characterized. *In vitro* data showed that basal levels of the major gemcitabine transporter – hENT1 – are directly correlated with the IC_{50} of the drug in a panel of 22 NSCLC cell lines,[65] although no clinical data to corroborate this finding have been reported. Growing interest has been generated by dCK, the rate-limiting enzyme in the biotransformation of gemcitabine. While pretreatment levels of dCK have not been associated with drug sensitivity, decreased dCK expression has been observed in a model of acquired resistance to gemcitabine, suggesting that dCK reinduction might restore sensitivity.[65] Interestingly, although no dCK-inactivating mutations have been described so far, recent findings suggest that dCK polymorphisms might influence dCK expression and, ultimately, gemcitabine activity in pancreatic cancer.[66,67] This observation, which should be extended to NSCLC patients, suggests dCK genotyping might help to identify sensitive/resistant subjects, although more robust data need to be produced.

Other biomarkers that have been studied include enzymes that might lead to early gemcitabine inactivation, like 5′-nucleotidase (5′NT), and CDA. While low levels of 5′NT have been observed in tumor cell lines resistant to gemcitabine,[68] a recent immunohistochemical study in 43 NSCLC patients with advanced disease indicated that low 5′NT expression is an independent predictor for increased survival for subjects exposed to the drug.[69] The limited sample size of the study precludes any firm conclusion and certainly deserves further investigation in larger cohorts of patients. Studies aimed at correlating CDA mRNA expression with outcome in gemcitabine-treated patients, particularly with pancreatic cancer, produced conflicting results.[70,71] Similarly, most of the reports that have investigated the role of CDA polymorphisms in predicting gemcitabine activity failed to show any association with drug activity,[72,73] although multiple findings seem to indicate that different CDA genetic variants might influence gemcitabine pharmacokinetics, with an ultimate impact on the toxicity of the compound.[74,75]

Being a major target of gemcitabine, RR has been widely investigated in cohorts of NSCLC patients treated with the drug, with specific attention for the RRM1 subunit.[76–79] Most of the studies showed that RRM1 mRNA expression was associated with significantly longer overall survival in patients who received a gemcitabine-based doublet both in the neoadjuvant and palliative setting,[76–79] while it represented a prognostic factor for decreased survival for patients who underwent surgery alone.[80] In addition, also RRM1 polymorphisms have been correlated with outcome in NSCLC patients treated with gemcitabine,[81] despite the lack of a clear association between different haplotypes and RRM1 expression.[81,82] These findings led investigators to perform a randomized phase II trial aimed at customizing treatment based on ERCC1 – a predictor for platinum compounds activity[83] – and RRM1 expression in 85 chemonaive NSCLC patients with advanced disease[84] Based on tumor expression of these two biomarkers, doublets including carboplatin, gemcitabine, vinorelbine and docetaxel were selected. This customized approach led to a response rate of 44% and to a disease-free and overall survival of 6.6 and 13.6 months, respectively, encouraging further evaluation of genomic-driven strategies in phase III trials.

Conclusions

Gemcitabine in association with cisplatin represents an active combination against NSCLC, and has been selected

as the reference regimen for the first-line setting in several European countries. The pivotal role of this doublet has been corroborated by robust pharmacoeconomic data addressing the cost-effectiveness of the GC regimen compared with other new generation platinum-based combinations. Advances in the molecular knowledge of cancer and the development of sophisticated biological assays have enabled the safe and effective combination of gemcitabine with different new targeted agents and the identification of biomarkers that might be potentially used for prospective patient selection. In fact, customized treatments represent the next big step that medical oncologists are trying to pursue, with the ultimate goal of offering cancer patients active and safe options in their battle against cancer.

Disclosure

The author declares no conflicts of interest.

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