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Abstract

Background Iniparib is a novel anticancer agent initially considered a poly (ADP-ribose) polymerase (PARP) inhibitor, but subsequently shown to act via non-selective protein modification through cysteine adducts. This randomized phase II study investigated the addition of iniparib to gemcitabine–cisplatin in metastatic non-small-cell lung cancer (NSCLC) patients.

Patients and methods Patients with histologically confirmed stage IV NSCLC were randomized 2 : 1 to receive gemcitabine (1250 mg/m^2, days 1/8) and cisplatin (75 mg/m^2, day 1) with [gemcitabine/cisplatin/iniparib (GCI)] or without [gemcitabine/cisplatin (GC)] iniparib (5.6 mg/kg, days 1/4/8/11) every 3 weeks for six cycles. The primary end point was the overall response rate (ORR). Secondary objectives included progression-free survival (PFS), overall survival (OS), and safety. The study was not designed for formal efficacy comparison, the control arm being to benchmark results against the literature.

Results One hundred and nineteen patients were randomized (39 GC and 80 GCI). More GCI patients were male (80% GCI and 67% GC) and had PS 0 (61% GCI and 49% GC). The ORR was 25.6% [95% confidence interval (CI) 13.0%–42.1%] with GC versus 20.0% (95% CI 11.9%–30.4%) with GCI, which did not allow rejection of the null hypothesis (ORR with GCI ≤20%; P = 0.545). Median PFS was 4.3 (95% CI 2.8–5.6) months with GC and 5.7 (95% CI 4.6–6.6) months with GCI (hazard ratio 0.89, 95% CI 0.56–1.40). Median OS was 8.5 (95% CI 5.5 to not reached) months with GC, and 12.0 (95% CI 8.9–17.1) months with GCI (hazard ratio 0.78, 95% CI 0.48–1.27). More GCI patients received second-line treatment (51% GC and 68% GCI). Toxicity was similar in the two arms. Grade 3–4 toxicities included asthenia (28% GC and 8% GCI), nausea (3% GC and 14% GCI), and decreased appetite (10% in each).

Conclusions Addition of iniparib to GC did not improve ORR over GC alone. The GCI safety profile was comparable to GC alone. Imbalances in PS and gender distribution may have impacted study results regarding PFS and OS.

Trial Registration ClinicalTrial.gov Identifier NCT01086254.

Key words

- iniparib
- non-small-cell lung cancer
- advanced disease
- first-line therapy

introduction

Iniparib (4-iodo-3-nitrobenzamide, BSI-201) was originally investigated as a poly (ADP-ribose) polymerase (PARP) inhibitor. However, later preclinical studies showed that it does not possess typical characteristics of PARP inhibitors, instead inducing cell response by non-selective modification of numerous proteins via cysteine adducts [1]. It is believed that iniparib acts as a pro-drug whose nitro-group is converted into either a nitroso-group or a nitrosyl radical by two alternative reduction processes. Proteomic and transcriptional profiling experiments and short-

hairpin RNA synergy screens are consistent with a mechanism, in which the Nrf2-mediated antioxidant response and/or the mitochondrial electron transport chain converts iniparib into its putative active metabolite. This metabolite was observed to uncouple electron transport from oxidative phosphorylation, leading to the production of reactive oxygen species at cytotoxic levels in an *in vitro* breast cancer model [2].

Despite promising data from an earlier phase II study, the addition of iniparib to a gemcitabine–carboplatin doublet failed to show a significant benefit in terms of the clinical benefit rate, overall response rate (ORR), progression-free survival (PFS), or overall survival (OS) in a phase III randomized study in metastatic triple-negative breast cancer patients [3, 4]. Iniparib administered either as a single agent or in combination with chemotherapy has shown a predictable and manageable safety profile at the proposed dose and schedule.

Standard of care systemic therapy for inoperable non-small-cell lung cancer (NSCLC) is platinum-based doublet chemotherapy. A survival benefit was reported in a meta-analysis comparing platinum agents combined with gemcitabine with other platinum doublets [5]. With a median OS of ~10 months in this population, additional therapeutic approaches are keenly awaited. The phase II study presented here investigated the potential benefit and safety of adding iniparib to the standard cisplatin (Bristol-Myers Squibb)–gemcitabine (Eli Lilly and Co) doublet for the treatment of metastatic NSCLC.

patients and methods

study design

This phase II, randomized, open-label, non-comparative study was carried out in five European countries between May 2010 and December 2011. Patients were randomized to gemcitabine 1250 mg/m^2 (days 1 and 8) plus cisplatin 75 mg/m^2 (day 1), with [gemcitabine/cisplatin/iniparib (GCI)] or without [gemcitabine/cisplatin (GC)] iniparib 5.6 mg/kg (1-h intravenous infusion, days 1, 4, 8, and 11) every 3 weeks for six cycles. A 2 : 1 randomization ratio in favor of GCI was used and randomization was stratified for histological type (squamous versus non-squamous) and smoking status (smoker versus never-smoker). Two dose reductions for gemcitabine or cisplatin were permitted for toxicity and a maximum 2-week treatment delay.

Hematology, biochemistry, and vital signs were evaluated on days 1 and 8 of every cycle. Adverse events were graded according to NCI-CTCAE, v4.0. Tumor evaluation was carried out at screening and then every 6 weeks until progression, death, other anticancer treatment, or study cutoff date. After treatment, patients were followed up for survival every 3 months until cutoff. Response was evaluated by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST, v1.1). A confirmatory scan was carried out in patients with complete response (CR) or partial response (PR) at least 4 weeks after the initial documentation of response. The study was approved by the local and national ethics committee and conducted in accordance with the Declaration of Helsinki.

patient eligibility

Patients had to be at least 18 years old and have histologically confirmed, squamous or non-squamous stage IV (UICC TNM 7th edition) NSCLC with no prior systemic therapy, measurable disease according to RECIST v1.1, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequate hematologic, renal, and hepatic function. Patients with prior definitive radiotherapy for locally advanced NSCLC were eligible. Patients with a history of cardiac disease or active brain metastases were not eligible. All patients gave written informed consent before enrollment.

statistical analyses

The study was not designed for formal comparisons of efficacy end points between arms, the control arm being used to benchmark results against available data for combined cisplatin–gemcitabine. For the GCI arm, 70 patients were needed to provide ~90% power to reject the null hypothesis that the true ORR with GCI was ≤20%, assuming the true response rate was 36%, using a one-sided exact binomial test at a significance level of 0.05. Thirty-five patients (50% of the GCI arm sample size) were planned in the control arm.

The ORR with the 95% confidence interval (CI) was calculated in the intent to treat (ITT) population (i.e. all randomized patients). PFS was defined as the time from randomization to progressive disease (RECIST) or death, whichever was earlier. In the absence of progression or death, patients were censored at the last tumor assessment before cutoff or starting other anticancer therapy. OS was defined as the time from randomization to death. In the absence of death, patients were censored at the cutoff date or the last date they were alive, whichever was earlier. PFS and OS were analyzed with the Kaplan–Meier method. The cutoff date was 1 year after the first dose of the last treated patient. Safety data were summarized with descriptive statistics in patients who received at least one dose of study treatment.

results

A total of 119 patients were randomized, 39 to the GC arm, and 80 to the GCI arm. Two patients randomized to the GCI arm were not treated due to protocol deviations. Patient and disease baseline characteristics are summarized in Table 1. Characteristics were mostly well balanced between the two treatment arms, although more GCI patients were male (80% GCI and 67% GC) and had PS 0 (61% GCI and 49% GC), while fewer GCI patients had an initial diagnosis of stage I or III (4% GCI and 10% GC). Median treatment duration was 13.9 weeks (range, 3–23 weeks) for the GC arm and 15.0 weeks (range, 3–23 weeks) with GCI. A median number of four cycles was administered in both arms, and a similar proportion of patients in each arm completed the six planned treatment cycles (41% GC and 45% GCI). Median relative dose intensity was 88% and 85% for gemcitabine in the GC and GCI arms, respectively, 85% for cisplatin in both arms, and 91% for iniparib.

Table 1.

Patient and disease characteristics at study entry, ITT population

antitumor activity

The ORR in the ITT population was lower in the GCI arm than in the GC arm: 20.0% (95% CI 11.9%– 30.4%) versus 25.6% (95% CI 13.0%– 42.1%), and did not allow rejection of the null hypothesis (ORR with GCI ≤20%; $P = 0.545$; Table 2). Best overall responses included 1 CR and 15 PRs in the 80 GCI patients and 10 PRs in the 39 GC patients. Stable disease was more frequent in the GCI arm than in the GC arm (55% versus 44%, respectively).

Table 2.

Summary of efficacy parameters, ITT population

survival

At the cutoff date, progression or death was reported in 32 GC (82.1%) and 52 GCI patients (65.0%). Median PFS was 4.3 (95% CI 2.8–5.6) months in the GC arm and 5.7 (95% CI 4.6–6.6) months in the GCI arm, with a hazard ratio (HR) of 0.89 (95% CI 0.56–1.40) favoring the GCI arm (Figure 1A). Fourteen GC (35.9%) and 33 GCI patients (41.3%) were alive at last contact. Median

OS was 12.0 (95% CI 8.9–17.1) months in the GCI arm and 8.5 (95% CI 5.5 to not reached) months in the GC arm, with an HR of 0.78 (95% CI 0.48–1.27; Figure 1B).
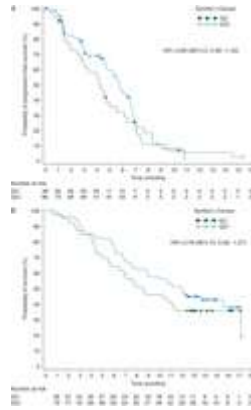

Figure 1.

Kaplan–Meier estimates of progression-free (A) and overall survival (B) in the ITT population, according to the treatment arm.

safety

Safety was analyzed in the 117 treated patients. Toxicity profiles were similar for the two arms (Table 3). Grade 1–2 hematologic toxicity was widespread, and approximately 50% of the patients had grade 3–4 events, notably neutropenia (44% GC and 37% GCI patients), including three GC patients with febrile neutropenia. Asthenia/fatigue and gastrointestinal toxicities were also frequent. Grade 3–4 toxicities included asthenia (28% GC and 8% GCI), nausea (3% GC and 14% GCI), decreased appetite (10% in both arms), vomiting and hypertension (8% in both arms), dyspnea (10% GC and 4% GCI), pulmonary embolism (8% GC and 6% GCI), and fatigue (5% in both arms). Differences between arms (including grade 3–4) were apparent for asthenia, nausea, dyspnea, hyponatremia, and febrile neutropenia, which were more frequent in GC patients, while pyrexia and abdominal pain were more common with GCI.

Table 3.

Main adverse events (NCI-CTCAE; >20% of patients and grade 3–4) and hematologic laboratory findings, safety population

Five patients died due to adverse events, three of which were treatment-related (two GC patients, one with septic shock and the other with mental status changes, and cardiac failure in a GCI patient). Seven GC (18%) and 16 GCI (21%) patients discontinued the study due to a wide range of AEs (mostly grade 3–4). AEs led to dose reductions in 56% of the patients and delay in approximately one-third, generally due to hematologic toxicity or asthenia (Table 4). Approximately half of the patients had at least one gemcitabine or iniparib dose omission.

Table 4.

Treatment modifications

therapy after GC or GCI treatment

Second-line therapy was given at the investigator's discretion and could be started before documented progression. More than half of the patients received further systemic therapy on-study (51% GC and 68% GCI; Table 5), notably pemetrexed (GC 18% and GCI 20%) and docetaxel (GC

18% and GCI 16%). In PFS analyses, more GCI patients were censored for initiating new antitumor therapy (22 patients, 27.5%) compared with GC (4 patients, 10.3%).

Table 5.

Therapy after GC or GCI treatment

discussion

Addition of iniparib to standard gemcitabine–cisplatin therapy did not improve the activity of this chemotherapy doublet in metastatic NSCLC patients in terms of the ORR (25.6%, 95% CI 13.0%− 42.1% with GC; 20.0%, 95% CI 11.9%−30.4% with GCI). The 25.6% ORR in the GC arm is close to the expected 28% rate [6], showing that patients enrolled in this study were representative of the targeted NSCLC population. The failure of iniparib to add clinical benefit in this context may be influenced by its mechanism of action which is different from that of PARP inhibitors [1]. Selection of PFS rather than ORR may have been a more appropriate end point for measuring benefit, the value of the latter having been questioned, notably in studies with targeted agents [7]. In addition, interpretation of the primary efficacy results may have been influenced by imbalances in various key baseline characteristics, such as PS, gender, and stage.

For the secondary efficacy parameters, median PFS was longer in the GCI than in the GC arm (5.7 versus 4.3 months, HR 0.89). However, median PFS in GC-treated patients was shorter than reported in phase III studies conducted in the same population (5.1–6.1 months) [6, 8–11]. Similarly, a marginal trend towards a survival benefit was seen with GCI (median OS of 12.0 versus 8.5 months with GC alone, HR 0.78). Though here again median OS in GC-treated patients was shorter than published reports (9.6–12.5 months). Median OS in this small study may have been confounded by other factors such as subsequent therapy or tumor heterogeneity. To date, no pharmacodynamic markers predicting efficacy have been identified.

The addition of iniparib did not significantly alter the GC safety profile, notably with respect to withdrawals due to toxicity, severe events, and reductions or delays for toxicity. Furthermore, most reported differences favored the GCI arm. Addition of iniparib did not impact the incidence of neutropenia or serious systemic infections, with no cases of febrile neutropenia in the GCI arm. The excess of severe asthenia/fatigue reported with GC may be due to the higher proportion of patients with PS 1 at baseline.

This proof-of-concept study was not designed for formal comparison of efficacy end points between the test and the control arms. The purpose of the control arm was to benchmark results against historical data. However, due to the lack of efficacy of the test arm and since the patient population was representative of the studied disease, a single-arm trial design would have led to a similar conclusion.

This trial enrolled patients approximately in parallel with a phase III study of gemcitabine and carboplatin with or without iniparib in patients with metastatic squamous NSCLC, the results of which were recently communicated as negative [12]. In conclusion, treatment of metastatic NSCLC patients with 5.6 mg/kg iniparib added to gemcitabine–cisplatin did not give benefit over the chemotherapy doublet alone, and no further clinical development of iniparib in this indication is planned.

funding

disclosure

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