A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease


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Background: This study compared irinotecan plus cisplatin (IP) with etoposide plus cisplatin (EP) in small-cell lung cancer patients with extensive disease.

Patients and methods: Patients were randomly assigned to receive cisplatin 80 mg/m² and either irinotecan 65 mg/m², days 1 and 8 or etoposide 100 mg/m², days 1–3, every 3 weeks.

Results: Baseline characteristics were balanced between patients receiving IP (N = 202) or EP (N = 203). Median overall survival was nonsignificantly superior for patients receiving IP versus EP, 10.2 versus 9.7 months [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.65–1.01, \( P = 0.06 \)] and 1- and 2-year survival rates were 41.9% versus 38.9% and 16.3% versus 8.2%, respectively. Noninferiority of IP versus EP was established, upper bound of the 95% CI of HR 1.01 (prespecified margin IP/EP < 1.25). Overall response (39.1% versus 46.6%) and time to tumor progression (5.4 versus 6.2 months) were not superior for IP. Grade 3/4 vomiting (10.9% versus 4.4%) and diarrhea (15.4% versus 0.5%) were more common in the IP versus EP arm; grade 3/4 neutropenia was more frequent in the EP (59.6%) versus IP arm (38.1%).

Conclusions: Our data demonstrate the noninferiority of IP versus EP for survival in primarily Western patients with SCLC-ED. A meta-analysis is required to finally assess the role of irinotecan in this setting.

Key words: cisplatin, etoposide, irinotecan, small-cell lung cancer with extensive disease

introduction

Lung cancer is the most commonly diagnosed cancer worldwide with an estimated 1.5 million new cases in 2007 [1]. Small-cell lung cancer (SCLC) accounts for 10%–15% of lung cancer cases and is responsible for up to 25% of annual deaths from the disease [2]. SCLC has an aggressive phenotype characterized by rapid tumor growth and early metastatic spread. The majority of patients with SCLC are classified as having extensive stage disease (SCLC-ED) at diagnosis [3]. Many chemotherapy regimens have proven active for patients with SCLC-ED; however, survival rates are generally poor with median survival of <12 months and 1- and 2-year survival rates of 35%–45% and 10%–20%, respectively, reported [4]. In most countries, etoposide in combination with cisplatin (EP) or carboplatin is considered the standard of care.

There is a recognized need for more active agents in the treatment of SCLC-ED. Preclinical studies have demonstrated irinotecan (a topoisomerase I inhibitor), displays synergism and no cross-resistance when combined with platinum agents [5, 6]. In 2002, the Japan Clinical Oncology Group (JCOG-9511) compared irinotecan in combination with cisplatin (IP) with EP in the first-line treatment of 154 randomized patients with SCLC-ED of a planned cohort of 230 patients [7]. Prolonged median overall survival (12.5 months versus 9.4 months, \( P = 0.002 \)) and a nonsignificantly higher 2-year survival rate of 19.5% versus 5.2% were observed in the...
IP treatment arm compared with the EP arm [7]. This was the only trial in >20 years to demonstrate a significant improvement in survival over the EP regimen. However, a randomized study conducted in the United States, Canada, and Australia failed to demonstrate a difference in overall survival between the IP and EP treatment arms (10.2 versus 9.3 months) [8]. Differences in treatment outcomes between Asian and Western populations and the small number of patients who were entered in a randomized study of JCOG-9511 were the main explanations for the failure to observe a survival difference in this study. Recently, a confirmatory Southwest Oncology Group trial using the same study design as JCOG-9511 reported comparable overall response and survival outcomes between the treatment arms, with less hematologic but more gastrointestinal toxicity with IP compared with EP [9].

The present study was designed to confirm superiority of overall survival in untreated patients with SCLC-ED receiving IP compared with EP in an international multicentre setting, following the presentation of the JCOG-9511 trial. In the event that superiority was not met, a test of noninferiority was planned with a prespecified margin of hazard ratio (HR).

patients and methods

major patient eligibility criteria

Patients had newly diagnosed histological or cytological proven SCLC-ED, were aged 18–75 years with a World Health Organization (WHO) performance status (PS) of zero to one, and adequate hematology, clinical biochemistry, and organ function. Patients had not received previous radiotherapy (excluding that for bone metastasis on diagnosis) or surgery on the primary tumor (other than palliative). Exclusion criteria included previous systemic chemotherapy or immunotherapy; chronic inflammatory bowel disease; bowel obstruction or history of extensive intestinal resection; symptomatic brain metastases; symptomatic peripheral neuropathy and neurohearing (except due to tumor mass); active infections; a history of malignancy within the past 5 years, other than curatively treated nonmelanoma skin cancer or cancer of the cervix (in situ); and preexisting ascites. Patients with any other severe medical conditions including myocardial infarction within 6 months before study entry, cardiovascular disorders, or a history of severe neurological/psychiatric disorders were also excluded, as were pregnant patients.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization good clinical practice guidelines.

study design and treatment

This was a multicenter, open-label, two parallel-group phase III study. Patients were randomly assigned and stratified by WHO PS to receive i.v. cisplatin 80 mg/m² on day 1 and either i.v. irinotecan HCl 65 mg/m² on days 1 and 8 or i.v. etoposide 100 mg/m² on days 1, 2, and 3. Treatment was repeated every 3 weeks and planned for a total of six cycles. During the study, the original starting dose of irinotecan (80 mg/m²) in the IP arm was reduced (to 65 mg/m²) on the basis of recommendation of the Independent Data Monitoring Committee following an interim review of the safety data on 78 patients in which four treatment-related patient deaths were reported in the irinotecan-containing arm. The data reported are from patients enrolled and randomized following a protocol amendment lowering the starting dose of irinotecan to 65 mg/m².

Treatments was discontinued on withdrawal of patient consent, disease progression, unacceptable toxicity, a treatment delay of >2 weeks, or major protocol violations, after which patients were followed up every 2 months for a minimum of 13 months.

The primary end point was overall survival and secondary end points included the overall response rate (ORR), the duration of response, duration of disease stabilization, the time to progression (TTP), and safety analysis.

assessments

Patient histories and informed consent were taken within 3 weeks before they were randomly assigned to treatment. Safety evaluations were carried out at baseline and on day 1 of each cycle. Lesions were assessed by computed tomography at baseline, every three cycles throughout the treatment period and during follow-up. Objective tumor response was assessed according to the RECIST [10]. A complete response (CR) or partial response (PR) was confirmed by repeat assessments no <4 weeks after initial assessment. For stable disease, measurements were carried out at least once after treatment initiation at a minimum interval of 6 weeks. Safety was evaluated using treatment-emergent adverse events (AEs) graded according to National Cancer Institute—Common Toxicity Criteria (NCI-CTC, version 2). The incidence of febrile neutropenia on the basis of grade 3 or 4 neutropenia reported by laboratory assessment accompanied by grade 1 or higher fever was determined. The incidence of infection, reported either as an infection or as a grade 2 or higher fever using the NCI-CTC criteria, was also determined.

statistical methods and considerations

The main analysis was a two-tailed unadjusted log-rank test of the superiority of overall survival in the experimental arm (IP) over the control arm (EP) at overall < =0.05. A total of 404 patients (202 per arm) were to be recruited to demonstrate a significant superiority of overall survival with an < =0.05 of 4.87% and a power of 80% at final analysis, assuming an increase in 1-year survival from 38% to 50% with an accrual period of 18 months and a minimum follow-up of 13 months. In the event that IP prolonged survival relative to EP, but the difference was not statistically significant, a test of noninferiority for survival in the IP arm over the EP arm was carried out, and noninferiority was to be claimed if the upper bound of the two-sided 95% confidence interval (CI) for the HR (IP/EP) estimated from a Cox proportional hazards model was <1.25. The overall type I error rate is preserved [11].

The full analysis population (FAP) was defined as all treated patients analyzed in the treatment arm to which they were randomly assigned; the per-protocol population (PP) consisted of a subset of the FAP comprising patients who were eligible, ‘assessable for response at baseline’, and without any major protocol deviations during the study. The cut-off for the analysis was set as the date of the 289th death. The number of deaths was 332 at the data cut-off date of 25 March 2008. Overall survival, TTP, and ORR were calculated for the FAP and PP. The safety population consisted of patients receiving at least one dose of treatment and was analyzed by the treatment received.

Time to event data were estimated using the Kaplan–Meier method [12] and compared using the log-rank test. The Cox proportional hazards model was used for the estimation of HRs. A comparison of tumor response rates was carried out using chi-square test with the odds ratio and 95% CI provided. Overall survival is the time from randomization until death. In this study, TTP is defined as the time from randomization to date of first documentation of radiologic progression or death due to any cause, which is currently more commonly referred to as progression-free survival (PFS). The ORR is obtained from the sum of the CR and PR and expressed as a percentage of patients assessable for response. The follow-up duration was defined as the time from which the patient was randomly assigned to treatment to the last contact date.
results

patient characteristics and demographics

From September 2003 to June 2007, 407 patients were enrolled from 59 centers across 12 countries: 203 were randomly assigned to receive IP and 204 to receive EP. Patient disposition is summarized in Figure 1. Ninety-seven patients receiving IP (48.0%) and 111 (54.7%) receiving EP completed six cycles of treatment. The most common reasons for early study discontinuation were AEs and death, which were slightly higher in patients receiving IP than EP. Patients discontinuing due to progressive disease were also slightly higher in those receiving EP compared with patients receiving IP. At the clinical cut-off date, 38 patients (18.8%) receiving IP were alive compared with 26 patients (12.8%) receiving EP. Patient demographics and disease characteristics at baseline were similar between the treatment arms (Table 1). Major patient protocol deviations were the same (8%) between the IP and EP treatment arms and included deviations from study inclusion criteria, respectively: age (1 versus 0), prior treatment (1 versus 0), clinical biochemistry (6 versus 3 patients), and timing of initial workup/clinical evaluation (6 versus 10). The PP population consisted of 176 and 186 patients in the IP and EP arms, respectively.

treatment received

One hundred and one (50%) patients receiving IP and 113 (56%) receiving EP were administered six cycles with 141 (70%) patients and 145 (71%) patients receiving at least four cycles, respectively. The dose intensities for all treatments received were similar between the treatment arms, as were the frequency of patients with dose reductions and infusion delays (Table 2). Reasons for dose reductions and cycle delays were also similar between the treatment arms.

efficacy

The majority of patients had died (82%) at the time of analysis. Median follow-up times were 31.6 months (range 9.6–50.9 months) and 31.7 months (9.5–51.1 months) in the IP and EP treatment arms, respectively. The efficacy data for the FAP is shown in Table 3. Overall survival favored patients receiving IP compared with EP although the difference was not statistically significant. The Kaplan–Meier estimates for overall survival for the treatment arms are shown in Figure 2. The upper bound of the 95% CI of the HR does not cross the prespecified noninferiority margin in either the FAP (HR 0.81, 95% CI 0.65–1.01, \( P = 0.06 \)) or PP (median overall survival 10.6 months versus 9.4 months, HR 0.75, 95% CI 0.60–0.94, \( P = 0.01 \)), demonstrating noninferiority of IP treatment compared with EP treatment. A Cox proportional hazards model for the effect of treatment on the risk of death adjusting for the stratification factors of WHO PS (0 versus 1 and 2) and center size (\( \geq 5 \) patients treated versus <5 patients treated) also supported the noninferiority of IP treatment (HR 0.64, 95% CI 0.33–1.22, \( P = 0.18 \)). An \textit{ad hoc} analysis using a Fleming–Harrington test shows improved overall survival in the IP arm compared with the EP arm for both the FAP and PP populations (supplemental Table 1, available at \textit{Annals of Oncology} online).

Figure 1. Patient disposition. FAP, full analysis population.
The confirmed CR rate was similar in the IP and EP treatment arms, and the ORR in patients receiving IP compared with patients receiving EP was not significantly different (Table 3). The median duration of response in the IP (n = 79) and EP (n = 94) treatment arms was similar: 5.5 months (95% CI 4.9–6.1 months) versus 4.9 months (95% CI 4.8–5.3 months) (HR 0.74, 95% CI 0.52–1.04, P = 0.08), and the median TtP in the IP and EP treatment arms were comparable.

There was no difference in the frequency of patients receiving additional antitumor therapy, 64.4% received further therapy in the IP arm compared with 67.0% in the EP arm, including chemotherapy (53.0% versus 57.6%), radiotherapy (38.1% versus 34.5%), and surgery (2.5% versus 0.5%). Two patients received further IP reinduction therapy and nine patients received further EP reinduction therapy; details of additional chemotherapy and radiotherapy are shown in supplemental Table 2 (available at *Annals of Oncology* online).
safety

Grade 3 or 4 treatment-related AEs were generally similar between the treatment arms (Table 4). However, patients treated with IP experienced more grade 3/4 diarrhea and more grade 3/4 vomiting than patients treated with EP, whereas grade 3/4 neutropenia was more common in patients receiving EP than IP. In the IP versus EP arms, the frequency of febrile neutropenia was 6.4% versus 9.9%, and infections was 21.8% versus 31.0% with grade 3 or 4 infection reported in 12.4% and 16.3% of patients, respectively. Permanent study discontinuations due to AE were similar in the IP (19.8%) and EP (14.3%) arms. The frequency of treatment-related serious AE was generally balanced between IP versus EP arms; however, diarrhea (15.8% versus 0%), vomiting (8.9% versus 2.5%), and nausea (6.9% versus 0.5%) were more common in patients receiving IP compared with EP and febrile neutropenia was slightly less common (3.3% versus 5.4%).

More patients receiving IP (27.7%) met criteria for definitive weight loss (≥5% of body weight) than those receiving EP (16%) and for those who lost ≥5% body weight, the median times to definitive weight loss were 42 and 46 days, respectively, both occurring at the beginning of the third treatment cycle. A similar frequency of patients in the IP and EP arms experienced worsening of PS (29.7% versus 25.6%), with the median times to definitive worsening of PS of 63.5 and 70.5 days, respectively.

Twenty-three patients (11.4%) in the IP arm and 14 (6.8%) in the EP arm died within 28 days of receiving last study medication with most patients dying due to malignancy (12 versus 9). Toxicity related to study treatment lead to the death of seven patients receiving IP [acute respiratory failure, general

Figure 2. Patient overall survival by treatment arm. Estimates are limited to 18 months of follow-up per patient. CI, confidence interval.

Table 4. Treatment-related adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Irinotecan + cisplatin (N = 202)</th>
<th>All grades</th>
<th>Etoposide + cisplatin (N = 203)</th>
<th>All grades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3/4</td>
<td>All grades</td>
<td>Grades 3/4</td>
<td>All grades</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (9.9)</td>
<td>137 (67.8)</td>
<td>11 (5.4)</td>
<td>115 (56.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (10.9)</td>
<td>120 (59.4)</td>
<td>9 (4.4)</td>
<td>79 (38.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35 (17.3)</td>
<td>123 (60.9)</td>
<td>1 (0.5)</td>
<td>18 (8.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0 (0)</td>
<td>21 (10.4)</td>
<td>1 (0.5)</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (6.9)</td>
<td>45 (22.3)</td>
<td>13 (6.4)</td>
<td>45 (22.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>77 (38.1)</td>
<td>110 (54.5)</td>
<td>121 (59.6)</td>
<td>135 (66.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (5.4)</td>
<td>28 (13.9)</td>
<td>9 (4.4)</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13 (6.4)</td>
<td>25 (12.4)</td>
<td>20 (9.9)</td>
<td>35 (17.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (7.4)</td>
<td>72 (35.6)</td>
<td>6 (3.0)</td>
<td>66 (32.5)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0 (0)</td>
<td>73 (36.1)</td>
<td>1 (0.5)</td>
<td>98 (48.3)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 (0.5)</td>
<td>32 (15.8)</td>
<td>1 (0.5)</td>
<td>34 (16.7)</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>3 (1.5)</td>
<td>33 (16.3)</td>
<td>2 (1.0)</td>
<td>31 (15.3)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>1 (0.5)</td>
<td>24 (11.9)</td>
<td>0 (0)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (3.5)</td>
<td>58 (28.7)</td>
<td>3 (1.5)</td>
<td>37 (18.2)</td>
</tr>
</tbody>
</table>

Data shown are n (%).

*Possibly related treatment-emergent adverse events, as judged by the investigator and reported in ≥10% of patients.

*Serum creatinine levels.
deterioration due to cisplatin, renal failure not otherwise specified (NOS), multiorgan failure, sudden death, dehydration, and diarrhea] and two patients receiving EP (infection NOS and increased serum creatinine, infection). The 60-day all-cause mortality rate was 10.4% for IP and 7.4% for EP.

**Discussion**

In the present study of previously untreated patients with SCLC-ED enrolled from predominantly European countries, overall survival was prolonged in those receiving IP compared with EP, although the difference was not statistically significant. However, the upper bound of the 95% CI (0.65–1.01) being within the prespecified noninferiority margin (1.25) for both the FAP and PP populations supports the noninferiority of IP [11]. These results remain consistent when excluding Asian patients (10 patients from Taiwan in total, 4 receiving IP and 6 receiving EP data not shown). A*  Ad hoc analysis using a Fleming–Harrington test also shows improved overall survival in the IP arm for both the FAP and PP populations.

This study is one of three [8, 9] undertaken in this setting following the publication of the JCOG-9511 trial. In these studies, the median overall survival in the EP arm was similar, ranging from 9.1 to 10.2 months and 1-year survival rates ranging from 34% to 35.2%, with an estimated 2-year survival rate of 8% in the trial by Hanna et al. [8, 9]. These findings are similar to those found here and in the JCOG-9511 trial [7]. Across these studies, the EP regimen was similar although in the trial by Hanna et al. [8], a lower dose intensity of cisplatin and higher dose intensity of etoposide were administered. In comparison with similar studies, the present trial achieved higher median survival and 2-year survival rates in the IP arm versus the EP arm (16% versus 8%,  \( P = 0.03 \)), although the hypothesized absolute survival advantage of 13% at 1-year was not met (42% versus 39%,  \( P = 0.56 \)) and equivalency of IP and EP can only be concluded. However, differences in the IP experimental regimen between studies were reported [7, 8, 13].

In the present study, the dose and schedule of irinotecan was the same as that described by Hanna et al. [8], but a slightly higher dose of cisplatin was administered. In contrast in the SO124 and JCOG-9511 trials, IP cycles were repeated every 4 weeks leading to lower dose intensities of irinotecan and cisplatin [9]. In addition, in studies of primarily Western patients with SCLC-ED, those with a WHO PS of two were ineligible whereas they represented 10% of patients in the JCOG-9511 study [7]. Furthermore, while treatment was planned for six cycles in the present study, the number of patients in each arm receiving four treatment cycles was balanced and comparable with previous reports where four treatment cycles were planned [8, 9].

Recently, carboplatin in combination with irinotecan (IC) or etoposide (EC) was compared in randomized studies of the patients with SCLC-ED [14–16]. A significantly superior median overall survival (8.5 months versus 7.1 months,  \( P = 0.02 \)) with an ∼30% reduced risk of death, and an increase in CR (18% versus 7%) in patients receiving IC compared with EC was reported by Hermes et al. [14]. The study design was markedly different from previous reports: the inclusion criteria were wide, with no limit on age and 50% of patients having a PS of two or more, which may explain the comparatively shorter overall survival times reported. A German phase II/III trial initially randomized 70 patients, demonstrated an encouraging improvement in PFS (9 versus 6 months,  \( P = 0.03 \)) for IC compared with EC [15]. In this trial, 17% of patients had a Karnofsky index ≤70 and the study drug doses and treatment schedules were different from the Hermes study [14]. Further, on randomizing 216 patients, no significant difference in median PFS or secondary end points were found, although a trend toward superior survival in the irinotecan arm was reported [16].

Studies comparing randomly assigned patients receiving the topoisomerase 1 inhibitor topotecan in combination with cisplatin (TP) with EP in patients with SCLC-ED have been carried out [17, 18]. Eckhardt et al. [17] assigned 784 patients to either TP or EP at the dose and schedule reported in previous randomized trials. No significant difference in median survival (TP, 9.2 months and EP, 9.4 months) was found although the predefined criteria for noninferiority of TP relative to EP was met in the 1-year survival rate. The ABC Study Group randomized 680 patients to EP or TP [18]. Median survival was longer in the experimental arm (10.3 months versus 9.4 months) although the difference was not statistically significant ( \( P = 0.30 \)). In both of these studies, hematological toxicity, especially thrombocytopenia and anemia, was higher although manageable in the experimental arm [17, 18].

Secondary efficacy end points in the present study were not significantly different between the treatment arms. Tumor response rates were similar to those previously reported [8] but lower than reported in other studies [7, 9]. This may reflect differences in study design between different trials, particularly the time between tumor assessments which if prolonged, as was the case in the present study, may lower confirmed responses and lengthen time to disease progression independent of treatment.

More gastrointestinal toxic effects were observed in the IP arm in this study compared with more hematological toxic effects in the EP arm. Previous trials in predominantly Western patients conclude that the IP regimen is tolerable with less hematological toxicity, but with a 15%–20% rate of grade 3/4 diarrhea, and a small toll of toxic deaths (≤5%) [8, 9]. In contrast, in the JCOG-9511 trial, grade 3/4 hematological toxic effects were frequent in both the EP and IP arms [7]. It is possible that the differences in efficacy and toxicity in these randomized trials may partly be due to racial and ethnic differences in the metabolism of irinotecan [19]. This may reflect population differences in the frequencies of polymorphic alleles that influence the function of genes involved in irinotecan transport and metabolism [9, 20, 21]. In Korean non-small-cell lung cancer (NSCLC) patients treated with IP, \( UGT1A1^{*6} \) alleles were found to be significantly associated with decreased tumor response and an increased incidence of severe neutropenia [22]. The potential impact of irinotecan dose, schedule, and dose intensity on efficacy and toxicity should also be considered [23, 24].

In NSCLC, direct comparisons of studies investigating old and new platinum-based doublet combinations are inconclusive regarding the expected survival benefit for the newer agents. Even where the current third-generation agents in combination with platinum drugs are widely accepted as standard therapy, meta-analyses of survival outcomes on this
subject continue to fuel debate [25–27]. A recent meta-analysis of randomized trials comparing first-line irinotecan plus platinum analogue versus etoposide plus platinum analogue in SCLC-ED demonstrated a significant survival benefit of IP over EP in Western patients (HR 0.86; 95% CI 0.76–0.97) [28]. A meta-analysis on the basis of individual patient data is required to definitively reject the nonsuperiority of the combination of topoisomerase I inhibitors and platinum compounds over etoposide and platinum compounds and to ascertain in the case of a statistical significant finding whether it is clinically relevant.

In conclusion, the present study, in accordance with other randomized trials in patients recruited from predominantly Western countries, failed to show a significant superiority in overall survival for the IP treatment regimen compared with the standard of care EP. However, IP treatment can be considered to be equally effective as the EP regimen, with a different toxicity profile. To date, there have been several studies comparing IP with EP in this setting and a meta-analysis of all individual patient data will be necessary to finally assess the role of irinotecan in the first-line treatment of patients with SCLC-ED.

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disclosure

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references