

Advances in our understanding of postoperative adjuvant chemotherapy in resectable non-small-cell lung cancer

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Purpose of review

After publication in 1995 of a meta-analysis of adjuvant chemotherapy in the treatment of NSCLC, a number of randomized trials investigated adjuvant chemotherapy using more active chemotherapeutic regimens and larger numbers of accrued patients per trial. This review will focus on recent clinical trials for adjuvant chemotherapy, and will help to interpret the applicability of these results to daily clinical practice.

Recent findings

Four large-scale randomized trials that used platinum-based chemotherapy have reported positive results during the last 3 years. These trials included cisplatin-based chemotherapy [the International Adjuvant Lung Cancer (IALT) trial], cisplatin plus vinorelbine [the National Cancer Institute of Canada (NCIC) BR10 trial], and carboplatin plus paclitaxel [the Cancer and Leukemia Group B (CALGB) 9633 trial]. More recently, another adjuvant trial [Adjuvant Navelbine International Trialist Association (ANITA)] was reported, which has added greatly to our understanding of the potential role of adjuvant treatment. Regarding adjuvant UFT (tegafur and uracil) chemotherapy, an individual patient data-based meta-analysis demonstrated its significant effect on survival in selected patients with completely resected non-small-cell lung cancer.

Summary

Recent trials indicate a survival benefit of postoperative adjuvant chemotherapy. These findings are anticipated to change the clinical management of patients with completely resectable non-small-cell lung cancer.

Keywords

adjuvant chemotherapy, cisplatin-based chemotherapy, non-small-cell lung cancer, UFT (tegafur and uracil)

Abbreviations

ALPI	Adjuvant Lung Project Italy
ANITA	Adjuvant Navelbine International Trialist Association
CALGB	Cancer and Leukemia Group B
CI	confidence interval
IALT	International Adjuvant Lung Cancer
JLCRG	Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy
NCIC	National Cancer Institute of Canada
NSCLC	non-small-cell lung cancer
UFT	tegafur and uracil

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Introduction

Although surgery is the optimal treatment strategy for curing patients with non-small-cell lung cancer (NSCLC), only one third of patients with NSCLC are candidates for surgery. The worldwide prevalence of lung cancer, however, is expected to exceed one million [1]. The prognosis of NSCLC depends on disease stage, but even in patients with stage I disease, approximately one third of patients will die of the disease within 5 years [2]. The majority of these relapses are distant metastases, and the risk of local recurrence after complete resection is quite low. Theoretically, postoperative chemotherapy is anticipated to eliminate occult micrometastases and improve overall survival. In an effort to overcome the poor outcome with surgery alone, numerous adjuvant chemotherapy trials have been conducted over the past three decades. This review will focus on clinical trials for adjuvant chemotherapy and will help to interpret the applicability of these results to daily clinical practice.

History of adjuvant chemotherapy trials

Earlier trials that generally investigated the role of alkylating agents and nonspecific immunotherapies uniformly failed to demonstrate any survival benefit of these therapies [3,4]. In the late 1970s, cisplatin-based chemotherapy was developed, and found to have activity against advanced NSCLC [5]. Several trials demonstrated a significant or marginal survival benefit of cisplatin-based adjuvant chemotherapy in patients at pathological stages I–III who underwent radical surgical resection [6,7]. In 1995, the NSCLC Collaborative Group conducted an individual patient data-based meta-analysis of 14 randomized trials involving 4357 patients [8]. The analysis revealed that cisplatin-based chemotherapy was

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associated with only a modest survival benefit over surgery alone [1394 patients in eight trials; hazard ratio = 0.87, 95% confidence interval (CI) = 0.74–1.02, $P = 0.08$]. Routine use of adjuvant chemotherapy was thus not recommended at that time, but further investigation was encouraged.

A new paradigm of adjuvant trials

After publication of the 1995 meta-analysis, a number of randomized trials investigated adjuvant chemotherapy using more active chemotherapeutic regimens and larger numbers of patients accrued per trial [9,10,11^{*},12,13,14^{*},15,16^{*},17^{**},18^{**},19,20^{**},21,22^{**}] (Table 1). Four large-scale randomized trials that used platinum-based chemotherapy have reported positive results during the last 3 years [17^{**},20^{**},21,22^{**}]. These trials included cisplatin-based chemotherapy {the International Adjuvant Lung Cancer (IALT) trial [17^{**}]}, treatment with cisplatin plus vinorelbine {the National Cancer Institute of Canada (NCIC) BR10 trial [20^{**}] and the Adjuvant Navelbine International Trialist Association (ANITA) trial [22^{**}]}, and treatment with carboplatin plus paclitaxel {the Cancer and Leukemia Group B (CALGB) 9633 trial} [21].

In the IALT trial [17^{**}], patients with tumors that were pathologically stage I–IIIA NSCLC were randomized postoperatively to receive either cisplatin-based chemotherapy or no chemotherapy. The decision to administer radiotherapy was agreed by the participating institutions. A total of 1867 patients were entered and randomized at 148 institutions in 33 countries. Cisplatin plus etoposide was the most frequently used chemotherapy regimen. A total of 27% of patients received postoperative radiotherapy. Grade 4 toxicities, including neutropenia, thrombocytopenia and nausea/vomiting, were observed in 23% of patients assigned to the chemotherapy arm, with seven treatment-related deaths (0.8%). Cisplatin-based chemotherapy yielded a statistically significant benefit, with 5-year survival rates of 44.5% versus 40.1% ($P < 0.03$) and 5-year disease-free survival rates of 39.4% versus 34.3% ($P < 0.003$).

The NCIC JBR10 [20^{**}] trial randomized 482 patients with stage IB or II NSCLC to postoperative chemotherapy with cisplatin plus vinorelbine or surgery alone, between 1994 and 2001. Cisplatin (50 mg/m²) was administered on days 1 and 8, and vinorelbine (30 mg/m²) on days 1, 8 and 15. In total, four chemotherapy cycles were planned. After initiation of the trial, the vinorelbine dose was reduced to 25 mg/m² because of hematologic toxicities. The survival time was significantly greater in the chemotherapy arm than in the surgery-only arm (5-year survival rate 69% versus 54%; $P = 0.0022$). This combination chemotherapy was generally well tolerated; principal toxicities were neutropenia, fatigue, and nausea and

vomiting. There were two treatment-related deaths (< 1%) noted in the chemotherapy arm.

In the CALGB9633 trial [21], 344 patients with stage IB NSCLC were randomized to receive either surgery alone or postoperative chemotherapy with carboplatin plus paclitaxel, which is frequently used for advanced-stage NSCLC. Both carboplatin and paclitaxel were administered on day 1 at AUC (area under the plasma concentration–time curve) = 6 and 200 mg/m² doses respectively. It is noteworthy that there were no treatment-related deaths among patients receiving chemotherapy, and that 85% of those allocated to the chemotherapy arm tolerated all four planned cycles of chemotherapy. The 4-year survival rate was significantly higher in the chemotherapy arm compared with the surgery-only arm (71% versus 59%; $P = 0.028$). This positive result is of particular interest, since many oncologists consider carboplatin-based chemotherapy to be better tolerated than cisplatin-based regimens in the treatment of NSCLC [23].

More recently, another adjuvant trial, ANITA, was reported [22^{**}], which has added greatly to our understanding of the potential role of adjuvant treatment. This trial randomized 840 completely resected patients with pathological stage IB–IIIA NSCLC to adjuvant cisplatin 100 mg/m² every 4 weeks plus vinorelbine 30 mg/m² weekly, or observation after surgical resection. Median follow-up time was longer than 70 months, and median overall survival was significantly prolonged in the adjuvant group compared with the surgery-alone group (65.8 versus 43.8 months). Subgroup analysis revealed that those with earlier stages of disease did not benefit from the adjuvant chemotherapy, which is consistent with the subgroup analysis in the IALT trial [17^{**}].

In contrast, negative results have also reported, including those of the Adjuvant Lung Project Italy (ALPI) trial [15]. The ALPI trial was a well-designed large phase III adjuvant trial that compared surgery plus a combination of cisplatin, mitomycin C and vindesine with surgery alone in 1209 patients with stages I–IIIA NSCLC. Median follow-up time was 65 months. This trial found no statistically significant difference in overall survival (hazard ratio = 0.96; 95% CI = 0.81–1.13).

There are several differences among the findings of the trials presented here. As shown in Table 1, these might be attributed mainly to differences in study design, patient selection and treatment administered. In particular, the contrasting results observed for the IALT and ALPI trials, despite the NSCLC patients having the same disease stage, are intriguing. One possible explanation is that the ALPI trial involved a three-drug regimen

Table 1 Adjuvant trials reported after the 1995 meta-analysis

Study	Year	No. of randomized points	Pathological stage	N2 positive (%)	Performance status 0-1 (%)	Chemotherapy regimen	Treatment compliance (%)	5 year survival (%) CH arm	5 year survival (%) OP arm	P (log rank)
Xu [9]	2000	70	I-III	NR	NR	CDDP + CPA + VCR + ADM + LOM + UFT	91	49	31	NS
Mineo [10]	2001	66	IB	0	100	CDDP + ETP	76	63	45	0.04
Nakagawa [11*]	2005	367	I	0	NR	UFT	51	82	76	0.11
Tada [12]	2002	172	I	0	99	UFT	77	75 ^a	58 ^a	0.04
Tada [12]	2002	95	II-III	54	98	CDDP + VDS then UFT	49	38	37	0.54
Endo [13]	2003	221	I-II	0	91	UFT	52	79	75	0.70
Imaizumi [14*]	2005	156	I	0	100	UFT	79	68	66	0.11
Imaizumi [14*]	2005	156	I	0	100	CDDP + VDS + UFT	61	88	88	
ALPI [15]	2003	1209	I-IIIa	25	100	CDDP + MMC + VDS	69	NR	NR	0.59
Waller [16*]	2004	381	I-IV ^b	21	93	CDDP + VDS or + VNR or + MMC + IFO or + MMC + VBL	64	58 ^c	60 ^c	0.90
IALT [17**]	2004	1867	I-III	26	92	CDDP + ETP or + VNR or + VDS or + VBL	74	45	40	< 0.03
JLCRG [18**]	2004	999	I	0	94	UFT	61	88	85	0.04
Tada [19]	2004	119	IIIA	100	100	CDDP + VDS	58	28	36	0.89
NCIC BR10 [20**]	2004	482	IB-II	0	100	CDDP + VNR	50	69	54	< 0.01
CALGB 9633 [21]	2004	344	IB	0	NR	CBDCA + PTX	85	71 ^d	59 ^d	0.03
ANITA [22**]	2005	840	IB-IIIa	35	95	CDDP + VNR	56 ^e	51	43	0.01

In the study of Tada *et al.* [12], patients with pathological stages I and II-III were accrued to separate trials. In the study by Imaizumi [14*], patients were randomly assigned to one of three arms, including the control arm. ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; JLCRG, Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy; NCIC, National Cancer Institute of Canada; CALGB, Cancer and Leukemia Group B; ANITA, Adjuvant Navelbine International Trialist Association; CH, chemotherapy; OP, surgery alone; NR, not recorded; CDDP, cisplatin; CPA, cyclophosphamide; VCR, vincristine; ADM, adriamycin; LOM, lomustine; UFT, uracil and tegafur, ETP, etoposide; VDS, vindesine; MMC, mitomycin; VNR, vinorelbine; VBL, vinblastine; CBDCA, carboplatin; PTX, paclitaxel.

^a8-year survival rate.

^bOnly two patients had pathological stage IV.

^c2-year survival rate.

^d4-year survival rate.

^eMedian percentage of planned dose.

Table 2 Statistical considerations in each trial

Factor	IALT (CDDP-based)	ALPI (CDDP + VDS + MMC)	NCIC JBR10 (CDDP + VNR)	ANITA (CDDP + VNR)
Statistical power (%)	90	80	80	90
Expected absolute improvement in 5-year overall survival (%)	5	7	10 ^a	10 ^b
α error	5% (one-sided) ^c	5% (two-sided)	5% (one-sided)	5% (one-sided)
No. of planned points	3300	1300	450	800
No. of accrued points	1867	1209	482	840

IALT, International Adjuvant Lung Cancer Trial Collaborative Group; ALPI, Adjuvant Lung Project Italy; NCIC, National Cancer Institute of Canada; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; JLCRG, Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy; CDDP, cisplatin; VDS, videsine; MMC, mitomycin C; VNR, vinorelbine; CBDCA, carboplatin; PTX, paclitaxel; UFT, uracil and tegafur.

^aExpected 3-year survival difference.

^bExpected 2-year survival difference.

^cThe trial was reformulated with a two-sided test, and this change provided the study with a power of 83 percent to detect a 5% difference in survival and a power of 90% to detect a 5.6% difference with the same sample size.

which may have been too toxic in the adjuvant setting and led to differences in patient treatment compliance between the two trials. The difference in numbers with regard to the frequency of postoperative radiotherapy between the two trials might also have led to a different result. Furthermore, the improvement in overall survival at 5 years was within the same range of benefit between the trials, but the IALT trial was larger and had greater statistical power, which might explain the different results (Table 2).

The oral chemotherapeutic agent UFT, which combines tegafur (a 5-fluorouracil prodrug) and uracil in a 1:4 molar ratio, has been extensively examined in Japan as an alternative to platinum-based chemotherapy. In 1996, Wada *et al.* [7] first reported that postoperative UFT administration improved the survival outcomes of patients with completely resected stage I–III NSCLC. Thereafter, five additional adjuvant randomized trials of UFT monotherapy were initiated (Table 1). The Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy (JLCRG) trial [18^{**}] was the largest trial, and accrued 999 patients with pathologically confirmed stage I adenocarcinoma. The reasons for selecting this subpopulation was that a significant survival benefit of UFT was only observed in those with adenocarcinoma histology in the previous study, and that most patients accrued in that study had pathological stage I disease [7]. The JLCRG trial showed that oral administration of UFT following complete resection significantly reduced recurrences and prolonged survival compared with surgery alone (5-year overall survival rates: 88 versus 85%; $P = 0.047$). UFT was well tolerated with few grade 3 toxicities (2%).

Meta-analysis of randomized trials

Hamada *et al.* [24^{**}] performed an individual patient-data-based meta-analysis using six trials comparing postoperative UFT monotherapy with surgery alone in 2003 patients with completely resected NSCLC. The patient characteristics were somewhat unique, in that the

numbers of female patients (45%) with stage I disease (95%) and adenocarcinoma (84%) were high. The analysis demonstrated that adjuvant UFT chemotherapy significantly improved overall survival (hazard ratio = 0.74, 95% CI = 0.61–0.88, $P = 0.001$). The 5-year and 7-year overall survival rates were 81.8% versus 77.2%, and 76.5% versus 69.5% respectively. The authors concluded that postoperative adjuvant UFT chemotherapy had a significant effect on survival in patients with completely resected NSCLC. Subgroup analysis of patients with T1N0 (stage IA) showed that only those with a tumor diameter exceeding 2 cm had a significant survival benefit with UFT monotherapy, which indicates that adjuvant chemotherapy may be less beneficial in patients with very-early-stage NSCLC, possibly because of their high survival rate with surgery alone.

We recently performed an abstracted-data-based meta-analysis of 11 randomized adjuvant trials involving 5711 patients reported after the 1995 meta-analysis [25^{*}]. Adjuvant chemotherapy was associated with a significant improvement in overall survival compared with surgery alone (hazard ratio = 0.872, 95% CI = 0.805–0.944, $P = 0.001$). In subgroup analyses, both cisplatin-based chemotherapy and UFT monotherapy showed a significant benefit, with hazard ratios of 0.891 (95% CI = 0.815–0.975) and 0.799 (95% CI = 0.668–0.957) respectively. Other meta-analyses have also demonstrated the benefit of adjuvant chemotherapy [26^{*}, 27^{*}]. These analyses, however, including ours, were based on abstracted data and not on individual patient data, which would give more reliable estimation than one based on abstracted data [28]. An individual patient-data-based meta-analysis is under way [29^{*}] and its results are eagerly awaited.

Application of the existing results to daily practice

It is reasonable to recommend adjuvant cisplatin-based chemotherapy for patients with completely resected NSCLC. The majority of randomized trials accrued

patients until 4–6 weeks after surgery [10,12,13,14*,15, 18**,19]. Therefore, only those in whom daily activities (that is, a good performance status of 0–1) had fully been restored within 4–6 weeks were considered to be good candidates for adjuvant chemotherapy. Cisplatin-based chemotherapy should not be recommended for patients with a poor performance status, for the following reasons. First, the IALT trial demonstrated a detrimental effect on survival in subgroup analysis [17**], and secondly, the majority of recent adjuvant trials accrued patients with a performance status of 0–1 (Table 1). Carboplatin-based chemotherapy is frequently used for advanced NSCLC, because of its better therapeutic index. In an adjuvant setting, carboplatin-based chemotherapy could also be given for four full cycles in 85% of patients [21], whereas completion of planned adjuvant cisplatin-based chemotherapy has been problematic (Table 1). The positive result observed in the CALGB trial [21], however, still seem to be preliminary, because of the short follow-up time (median of 34 months). Thus, in spite of the high treatment compliance, we would like to wait for the long-term results of that study to confirm the survival benefit of carboplatin-based chemotherapy.

Regarding UFT monotherapy, the concept of low-dose, mild and continuous treatment is very attractive. Furthermore, UFT can be administered orally to outpatients. Based on its favorable efficacy for early-stage NSCLC [24**], this drug might be beneficial especially for stage IB adenocarcinoma patients in daily clinical practice in Japan, where UFT has already been approved. There are several critical points to be noted, however. First, the UFT trials were all conducted only in Japan [7,11*,12,13, 14*,18**], and the activity and safety of anticancer agents may differ between Japanese and non-Japanese patients. One example is the ethnic differences in efficacy and toxicity profiles between populations with regard to the carboplatin plus paclitaxel combination [30] and gefitinib monotherapy [31]. Thus the same conclusion for UFT might not hold true outside Japan. In addition, a complicating factor is that the overall survival curves of the two arms overlapped up to 4 years in the JLCRG trial [18**], but the authors offered no clear-cut explanation for this finding. Thirdly, UFT has little activity against advanced NSCLC, with only a 6% response rate reported

Table 3 Questions on postoperative adjuvant chemotherapy remaining to be answered

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- (a) At which stage will patients benefit most from postoperative adjuvant chemotherapy?
 (b) Which drug should be combined with cisplatin?
 (c) How efficacious are other agents as adjuvant therapy?
 (d) Which is the superior treatment, adjuvant chemotherapy or neo-adjuvant chemotherapy?
 (e) Are biological molecular markers predicting those who will benefit from adjuvant chemotherapy available?
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[32]. Although there is no evidence clearly explaining the difference in UFT activity against early compared with advanced NSCLC, its benefit in patients with early-stage disease may be attributable to the anti-angiogenic effect of UFT [33]. Another postulated reason for UFT activity includes a preventative effect of UFT against the development of second primary malignancies. In the studies of Wada *et al.* [7], it is of note that the incidence of death from second primary tumors seemed to be lower in the UFT arm than in the control arm (1.9% versus 5.1%), although further confirmation is required. From all the points of view, there seem to be several issues that need to be answered in relation to UFT monotherapy in an adjuvant setting, in spite of the positive data available.

Future considerations

Several issues remain unresolved (Table 3). First, at which stage will patients benefit most from postoperative adjuvant chemotherapy, although positive adjuvant trials include those with stages I–III [17**,18**,20**,21,22**]? The CALGB (carboplatin plus paclitaxel) trial, which showed significant survival benefits, accrued stage I patients [18**,21], whereas subgroup analyses of the IALT, NCIC BR10 and ANITA trials demonstrated that those with earlier stage of disease unlikely benefited from the adjuvant chemotherapy [17**,20**,22**] (Table 4). The results of an updated individual patient data meta-analysis are expected to address the issue of appropriate candidates for adjuvant chemotherapy.

The optimal drug to combine with cisplatin remains to be determined in the setting of adjuvant use. Cisplatin plus one of the new agents was reported to yield a

Table 4 Subgroup analysis of the positive adjuvant trials

Pathological stage	IALT (CDDP-based)	NCIC JBR10 (CDDP + VNR)	ANITA (CDDP + VNR)	CALGB (CBDCA + PTX)	JLCRG (UFT)
IB	No	No	No	Yes	Yes
II	No	Yes	Yes	ND	ND
IIIA	Yes*	ND	Yes	ND	ND

*Yes indicates that patients at the indicated pathological stage benefited from adjuvant therapy; ND indicates that analysis was not done. IALT included patients with pathological stages IIIA and IIIB. IALT, International Adjuvant Lung Cancer Trial; NCIC, National Cancer Institute of Canada; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B; JLCRG, Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy; CDDP, cisplatin; VNR, vinorelbine; CBDCA, carboplatin; PTX, paclitaxel; UFT, uracil and teagafur.

Table 5 Ongoing adjuvant trials

Trial or group	Pathological stage	Treatment arms (chemotherapy regimens)
ANITA-2	I–IIIA	Surgery alone versus surgery then vinorelbine
NCIC BR19	IB–IIIA	Surgery then placebo versus surgery then gefitinib
NATCH	IA–IIIA ^a	Surgery alone versus surgery then carboplatin + paclitaxel versus carboplatin + paclitaxel then surgery
WJTOG	IB–IIIA	Surgery then UFT versus surgery then gemcitabine
Okayama	IB–IIIA	Surgery then carboplatin + paclitaxel versus surgery then UFT

ANITA, Adjuvant Navelbine International Trialist Association; NCIC, National Cancer Institute of Canada; NATCH, (Neo) Adjuvant Taxol/Carboplatin Hope; WJTOG, West Japan Thoracic Oncology Group; UFT, tegafur and uracil.

^aClinical stage IB–IIIA (T3N1) and IA (tumor size > 2 cm).

significant survival advantage, compared with cisplatin plus older agent, in patients with advanced NSCLC [34]. Among the new drugs, vinorelbine was used in the two positive trials (the NCIC BR10 and ANITA trials). Thus one can consider that its combination is one of promising regimens.

Recently, neo-adjuvant chemotherapy has increasingly been considered as one of the most promising modalities for operable patients [35]. It remains unclear, however, whether adjuvant chemotherapy is more beneficial than neo-adjuvant chemotherapy. The NATCH [(Neo) Adjuvant Taxol/Carboplatin Hope] trial was designed to randomize 600 patients with clinical stage I–IIIA NSCLC into three arms: surgery alone, neo-adjuvant chemotherapy with carboplatin plus paclitaxel followed by surgery, and surgery followed by adjuvant chemotherapy with carboplatin plus paclitaxel (Table 5). This trial is considered to be important, because its results will hopefully elucidate the most appropriate treatment modality for operable patients.

Finally, an important issue is whether biological molecular markers, predicting the efficacy of adjuvant chemotherapy, are available. Although several markers, including p53, Ki-67, and K-ras, have been widely investigated, no definitive conclusion has yet been reached [15]. Further investigations that focus on these issues are required in order to develop tailor-made adjuvant chemotherapies.

Conclusion

Herein, we have discussed the advantages of adjuvant chemotherapy and its applicability in daily practice. Although postoperative chemotherapy was considered to offer little benefit until 1995, recent trials indicate a survival benefit associated with postoperative adjuvant chemotherapy. These findings are anticipated to change the clinical management of patients with completely resectable NSCLC. Since several clinical trials aimed at defining further the role of postoperative chemotherapy are ongoing, we anticipate the generation of further important information regarding the most suitable patient population and optimal chemotherapy regimens.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 210).

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